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British Journal of Anaesthesia

14

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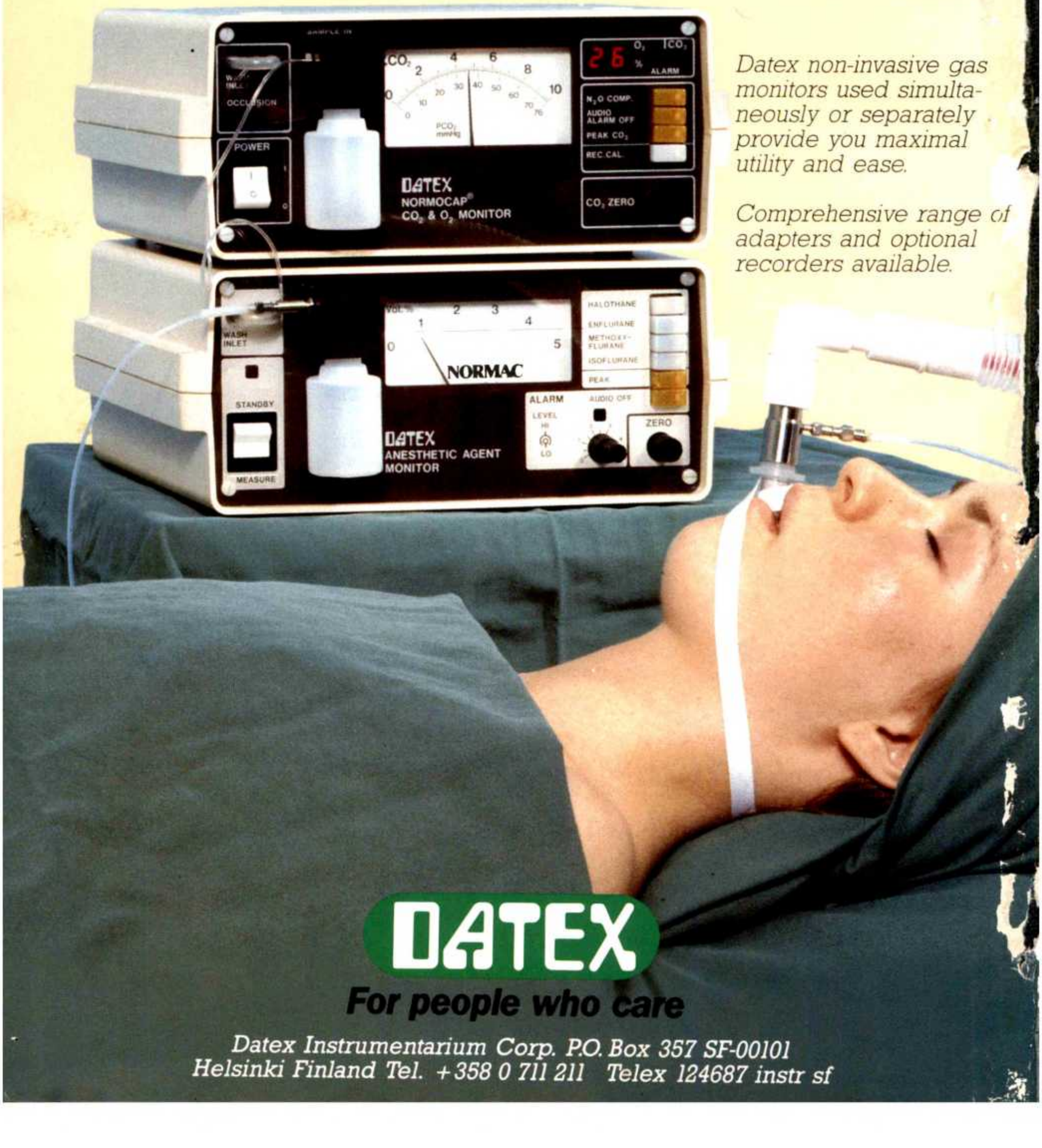

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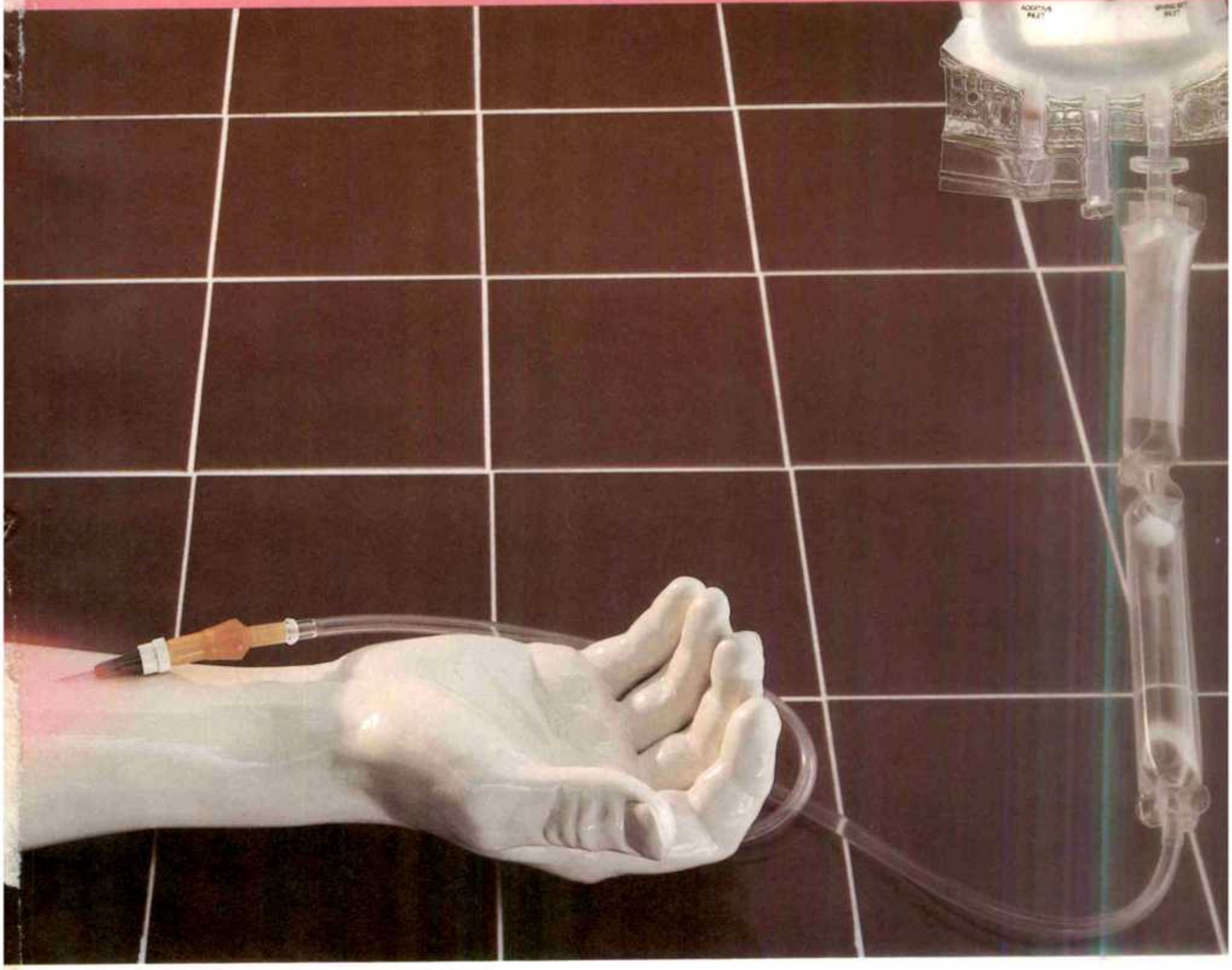

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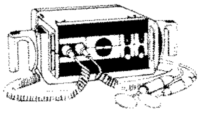
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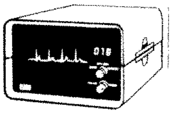
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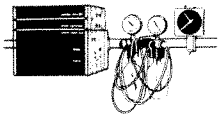
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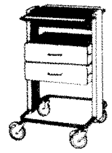
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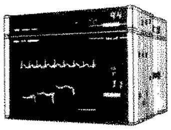
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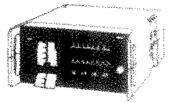
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ERRATUM

Br. J. Anaesth. (1986), **58**, 760

"Local Anaesthetic Techniques in Paediatric Surgery"

The doses of local anaesthetic agents recommended by Armitage (1979) have been given incorrectly on p. 769 of this article (left-hand column, under the equation). The correct doses are:

0.5 **ml** kg^{-1}, 1 **ml** kg^{-1} and 1.25 **ml** kg^{-1}, respectively.

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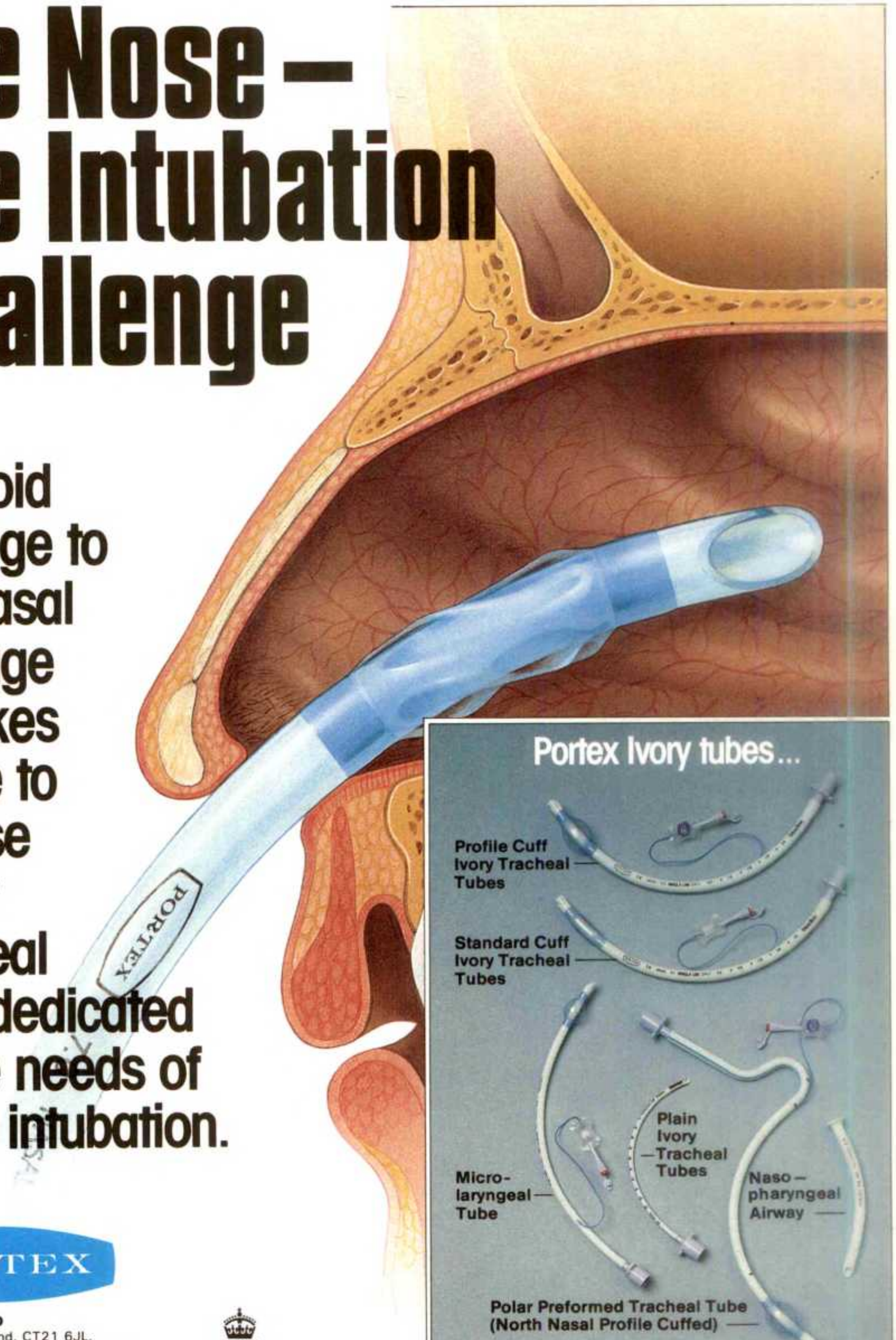
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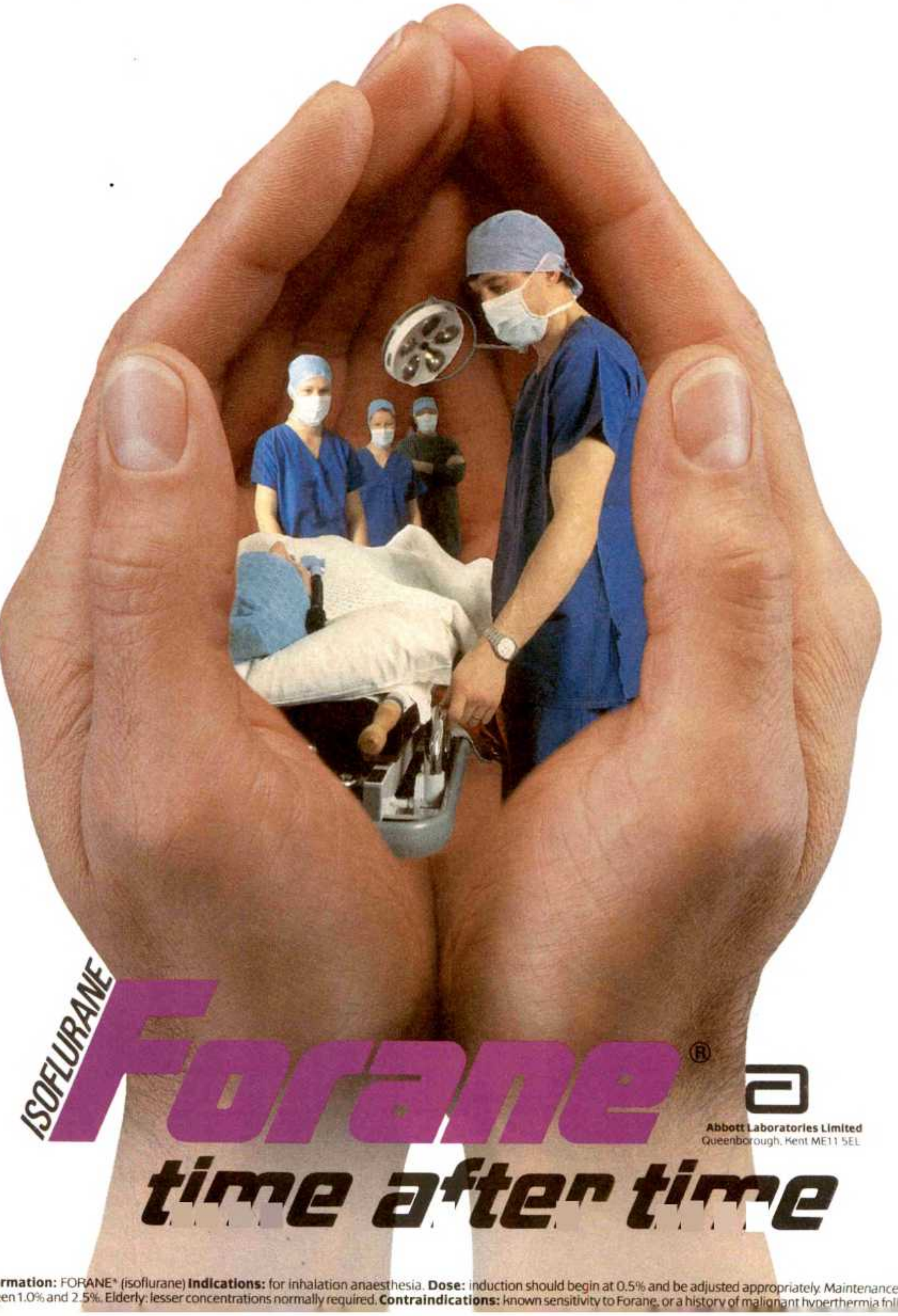

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escribing Information: FORANE* (isoflurane) **Indications:** for inhalation anaesthesia. **Dose:** induction should begin at 0.5% and be adjusted appropriately. Maintenance concentrations nerally lie between 1.0% and 2.5%. Elderly: lesser concentrations normally required. **Contraindications:** known sensitivity to Forane, or a history of malignant hyperthermia following a previous

"*I would have everie man write what he knowes and no more.*"—MONTAIGNE

BRITISH JOURNAL OF ANAESTHESIA

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EDITORIAL

COMPLICATIONS AND MEDICO–LEGAL ASPECTS OF ANAESTHESIA

One of the major problems facing the medical profession at the present time is the increasing volume of litigation to which it is exposed as a result of patients' attempts to gain damages for alleged or actual injury arising during the course of treatment. This is a worldwide phenomenon and a source of discussions on how to restrict damages to reasonable levels, and contain rapidly increasing subscriptions to medical defence organizations at the same time as providing just compensation for injury arising from accident or medical negligence. One of the few potential solutions currently under debate is the adoption of no-fault compensation for personal injury, although it will be clear from this Symposium Issue that this proposal is not without disadvantages.

Anaesthetists are in the relatively unusual position of administering lethal drugs to patients and manipulating the physiology of the respiratory and cardiovascular systems, in ways which are also potentially lethal, for reasons which are not primarily therapeutic. Because the purpose of anaesthesia is to permit a separate discipline to undertake patient treatment, it is easy to understand why the lay public should expect a higher standard of safety from anaesthesia than from surgery.

The results of several recent surveys suggest that the mortality rate resulting primarily from anaesthesia is of the order of 1:10000. This is a risk which would probably be regarded by many patients as acceptable in the light of anticipated benefits from proposed surgery. This level of anaesthetic-related mortality is impressive (in contrast with a surgical mortality rate which may be 100 times greater). However, it is well to remember that this degree of safety has been achieved in only relatively recent times.

In the era of James Young Simpson, the combined surgical and anaesthetic mortality attributed to treatment such as amputation was approximately 30%. Caesarean section was practised rarely as it carried a mortality rate of 84% shortly before the introduction of antisepsis, which commenced with the use of carbolic acid by Lister in 1865.

In these early days, there was only a very small number of deaths related to anaesthesia, but the volume of surgery was also very small. Subsequently, there was a progressive increase to a peak of 916 anaesthetic-related deaths in England and Wales in the year 1938, associated with a parallel increase in the number of operations performed. However, there was a progressive increase in the magnitude and complexity of surgery, so some improvements did occur. For example, abdominal surgery was rarely practised until after the introduction of antisepsis, since it was invariably fatal.

From 1938 onwards, there was a progressive decrease both in the absolute number of anaesthetic-related deaths and in mortality rate. Sykes (1960) concluded that the events responsible for this dramatic change probably included: the appointment in 1937 of the first U.K. Chair of Anaesthesia in the University of Oxford, with the subsequent stimulus to effective teaching and research; the increasing availability of blood transfusion, stimulated by the trauma of the Second World War; the increased number of trained anaesthetists, which was boosted enormously by the introduction of the National Health Service in 1948; and the introduction during the the Second World War of neuromuscular blocking drugs which permitted the use of very light anaesthesia.

The purpose of this Symposium Issue on Complications and Medico–Legal Aspects of Anaesthesia is to draw the contemporary picture of anaesthetic-related hazards and complications. More recent studies of anaesthetic-related morbidity and mortality are reviewed and the problems and pitfalls in the interpretation of the data are described. This Symposium also draws attention to the medico–legal position in which the anaesthetist finds himself in the U.K., the U.S.A. and New Zealand.

The most important aspect of this subject relates to the maintenance of, and improvement in, anaesthetic safety. Factors commonly suggested as contributing to anaesthetic mortality include inadequate assessment and preparation of patients in the preoperative period, inadequate supervision in the intraoperative period, and inadequate patient supervision and management after operation. Attention to these points centres on maintaining the highest standard of training in anaesthesia and examining factors involved in lapses in vigilance and judgement by otherwise competent practitioners. Another important problem alluded to frequently is an inadequate degree of monitoring.

Many aspects of this wide and very important subject are discussed in this Symposium. Further information should be forthcoming from the recently completed Confidential Enquiry into Perioperative Deaths conducted jointly by the Association of Anaesthetists and Association of Surgeons of Great Britain and Ireland. It is hoped that the data obtained, which are currently under analysis, will provide further guidance towards maintenance and even improvement in operative safety, both anaesthetic and surgical.

G. Smith and J. Norman

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A REVIEW OF STUDIES OF ANAESTHETIC RISK, MORBIDITY AND MORTALITY

M. C. DERRINGTON AND G. SMITH

In recent years, there has been increasing interest in the development of risk assessment in anaesthesia, in order to improve the quality of care in anaesthetic practice by defining either the individual patient at increased risk of anaesthesia, or specific areas of anaesthetic practice which account for the more common causes of morbidity and mortality. Investigations in these areas are frequently dependent upon epidemiological methods of research, consideration of which lies outside the scope of this article. However, the reader is referred to an excellent article by Farrow and Fowkes (1986) in the recently published book *Epidemiology in Anaesthesia.*

This review of anaesthetic morbidity and mortality will be considered under four headings:

(1) Investigation of specific complications in anaesthesia in order to determine their cause.

(2) Study of individual risk factors present before operation in order to assess operative risk.

(3) Studies of "near misses" and of anaesthetic incidents (including critical incident studies and departmental near miss studies).

(4) Epidemiological studies of anaesthetic morbidity and mortality.

INVESTIGATION OF SPECIFIC COMPLICATIONS IN ANAESTHESIA IN ORDER TO DETERMINE THEIR CAUSE

Case reports in the literature offer little insight to the magnitude or frequency of anaesthetic problems, but they are valuable in two important ways, both of which have some bearing on morbidity and mortality. First, they provide advice to the anaesthetist on the management of patients with rare disorders. Second, they may reveal a previously unidentified complication producing morbidity or mortality in anaesthesia. This may be illustrated by such examples as bupivacaine cardiotoxicity and suxamethonium-induced cardiac arrest.

IVRA with bupivacaine

The introduction of bupivacaine was followed by recommendations for its use in i.v. regional analgesia (IVRA) (Ware, 1979; Ben Aronson and Vatashsky, 1980; Gooding et al., 1981). The drug was said to be safe and effective and to produce some degree of analgesia after the cuff was released at the end of the operative procedure, although there was some disagreement on whether or not it was the agent of choice for IVRA (Wildsmith, Scott and Brown, 1979). Soon afterwards three deaths occurred as a result of inadvertent cuff release shortly after the administration of the drug. These were publicized as hazard warnings (HN(82)7) in May 1982 and also recorded in the national press. There was some discussion on the mechanisms involved in the deaths (Davies, Gill and Weber, 1981; Ware, 1982; Wildsmith, 1982). Strong opinions were voiced on the efficacy of bupivacaine by the i.v. route (Wildsmith, Scott and Scott, 1980; Heath, 1982; Wildsmith, 1982). In order to examine the reliability of tourniquets, studies were conducted using radio-opaque dyes injected at different speeds and in different volumes, and serum concentrations of bupivacaine were measured before cuff release (Rosenberg et al., 1983). In addition, *in vivo* and *in vitro* investigations of the effect of protein binding on toxicity were reported. These investigations culminated in editorial comment which discredited the use of bupivacaine by the i.v. route.

Suxamethonium and burns

Unexpected cardiac arrest was mentioned in an account of the complications of burns submitted for publication in June 1957 (Moncrief, 1958). It was suggested that the burned patient was

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susceptible because of general debility and physiological derangement. Five episodes of cardiac arrest were described, all but one having occurred on induction of anaesthesia. One year later, an account was published (Finer and Nylen, 1959) of cardiac arrest in a burned patient on induction of anaesthesia for his fourth and sixth operations. He had received identical anaesthesia on three occasions previously; the fifth anaesthetic had been different in that the trachea had not been intubated. Similar events were reported in the following years (Forrest, 1959; Fleming et al., 1960; Allan, Cullen and Gillies, 1961).

The incidence of cardiac arrest during induction of anaesthesia in the burned patient was estimated at 1 in 209 compared with 1 in 2744 in other patients undergoing plastic surgery (Finer and Nylen, 1961). The danger period for the occurrence of cardiac arrest on induction of anaesthesia was noted as 21–50 days after burns were sustained (McCaughey, 1962).

Various mechanisms were postulated at this time, including vagal reflexes and potassium fluxes (Bush, 1964; Belin and Karleen, 1966). Definitive evidence was obtained when serial serum electrolyte concentrations were measured and the magnitude of the increase in serum potassium with ECG changes of hyperkalaemia were found to correlate with the dose of suxamethonium administered (Tolmie, Joyce and Mitchell, 1967).

There are many other examples of how case reports lead to formal investigation of mechanisms of morbidity or mortality. One which still defies totally conclusive evidence for the mechanisms involved is hepatic damage associated with halothane anaesthesia, probably because of the rarity of the condition (Spence, 1986).

STUDY OF SPECIFIC RISK FACTORS PRESENT BEFORE OPERATION IN ORDER TO ASSESS OPERATIVE RISK

Since anaesthesia is contemplated rarely without an operative or investigative procedure, review of anaesthetic morbidity and mortality should encompass investigation of preoperative and operative risk factors in the context of pre-existing disease. It is thus the investigation of factors which can be elicited before operation and which have a bearing on morbidity and mortality that are discussed in this section. Whilst precision is possible in predicting the likelihood of events occurring after operation in a population of patients, unfortunately this accuracy does not extend to an individual patient; this represents one of the most disappointing aspects of this type of work (Goldstein and Keats, 1970). However, there are three valuable facets of these data:

First, in patients with severe medical disease and surgically remedial problems, the data may be the basis for a decision to adopt alternative medical therapy or less extensive surgery. An illustrative example may be taken from a study by Del Guercio and Cohn (1980) who, using invasive techniques for the preoperative assessment of cardiovascular and respiratory function, found severe abnormalities in more than 20 of 148 elderly patients scheduled for major surgery. Eight of these underwent operation as originally planned and all died. Lesser procedures or alternative medical management were undertaken in the others, with better results. This example introduces the concept of the inoperable patient as opposed to the inoperable disease.

Second, these data may be the basis for recommendations (and improvement) in preoperative preparation, operative techniques and postoperative care. An example may be obtained from the work of Milledge and Nunn (1975) which, although based on a small number of patients, offers guidelines on management of patients with obstructive lung disease dependent on three preoperative tests of lung function. In 12 patients with severe chronic obstructive lung disease who underwent 15 operations, forced expiratory volume in 1 s, vital capacity and arterial blood-gas tensions were measured. The group with low ventilatory capacity but normal blood-gas tensions required no special treatment except physiotherapy and antibiotics. A second group with hypoxaemia in addition required more prolonged oxygen therapy after operation and a third group with hypoxaemia and hypercapnia needed postoperative ventilatory support.

Third, although the data do not predict for the individual patient, they do provide some guidelines. This is of increasing importance, especially in the United States where there are medico–legal implications in not explaining operative and anaesthetic risks to the patient. "The law penalises the anaesthetist when a complication occurs only when the possibility of its occurrence was not considered, watched for, recognised, treated promptly and appropriately or not explained beforehand that such a complication might occur if it were a material risk" (Forrest, 1984).

TABLE I. *The ASA Physical Status Scale*

Class I	A normally healthy individual.
Class II	A patient with mild systemic disease.
Class III	A patient with severe systemic disease that is not incapacitating.
Class IV	A patient with incapacitating systemic disease that is a constant threat to life.
Class V	A moribund patient who is not expected to survive 24 h with or without operation.
Class E	Added to any patient for emergency operation.

Lunn and Mushin (1982) emphasized the failure of anaesthetists to identify before operation patients at risk, with consequent inappropriate anaesthetic management—in 10% of the deaths included in their enquiry, the patient had not been seen before operation by an anaesthetist.

PREOPERATIVE RISK ASSESSMENT

Ideally, any method of predicting before operation the subsequent operative and postoperative course of a patient should be applicable to large numbers of patients, easy to peform, reproducible and inexpensive. Although there has been considerable effort directed recently into preoperative risk screening, only the ASA grading is applied widely at present.

The ASA Grading (table I)

This was introduced by Saklad (1941) to facilitate the tabulation of statistical data in anaesthesia. The author stated emphatically that it was not an estimate of operative risk. Obviously, it cannot be applied alone as a predictive factor for anaesthetic risk; it has been noted elsewhere (Goldstein and Keats, 1970; Keats, 1978) that there is no allowance for inclusion of criteria such as those for difficult intubation or family history of malignant hyperpyrexia. However, there is overall a relationship between ASA grading and perioperative mortality (table II) (Vacanti, Van Houten and Hill, 1970). In spite of its drawbacks, the ASA rating remains one of the few truly prospective and widely applied descriptions of the patient, with the exception of age and sex.

Although it has been suggested (Owens, 1978) that there is a great deal of discrepancy in classification of the same patient by different anaesthetists and also that the extent of the anticipated surgery may increase the grading (Saklad, 1941), there is evidence to suggest a surprising degree of agreement (Keats, 1978). After studying the predictors of cardiac mortality, Goldman (1978) pointed out that the ASA scale was probably the best available predictor of non-cardiac deaths and a fair predictor of cardiac deaths. This is perhaps not unexpected, since sicker patients are more likely to die.

The grading is used today in much the same form as originally described except that, instead of categories VI and VII an E is appended (table I) (Classification, 1963).

Gender

Several investigators (Beecher and Todd, 1954; Phillips et al., 1960; Pederson et al., 1986) have observed that males present greater anaesthetic risks than do females. The reasons advanced for this include the large number of minor gynaecological procedures in women and that men tend to have more severe heart and lung disease (Dripps, Lamont and Eckenhoff, 1961), although the observation remains valid in consideration of similar operations in similar age groups (Gordh, 1950).

Cardiac disease

The risk factors and the optimum management of the patient with heart disease scheduled for surgery have been extensively investigated. The existence of silent myocardial infarction (Driscoll et al., 1961) and the importance of screening for its occurrence for up to 6 days after operation are well documented, although the reported incidence

TABLE II. *Mortality rates for each ASA physical status—emergency and elective cases. (From Vacanti, Van Houten and Hill (1970))*

ASA rating	Anaesthetic procedures	Deaths	Mortality rate (%)
I	50 703	43	0.08
II	12 601	34	0.27
III	3626	66	1.8
IV	850	66	7.8
V	608	57	9.4
Totals	68 388	266	0.39

varies widely from 21% of 62 postoperative myocardial infarctions (Tarhan et al., 1972) to 100% of three postoperative infarctions (Hunter et al., 1968). It is widely accepted that the mortality of myocardial infarction occurring after operation is much higher than normal (Tarhan et al., 1972).

Cardiac risk factors in the patient with heart disease scheduled for non-cardiac surgery have been examined by multivariate discriminant analysis and a scoring system (table III) has been devised according to their relative importance (Goldman et al., 1977). These risk factors were later validated in prospective studies (Goldman et al., 1978).

The risk of cardiac problems including myocardial reinfarction and the subsequent high mortality rates have been found by different centres to be very similar when operative procedures are carried out within 3 and 6 months of myocardial infarction (Topkins and Artusio, 1964; Tarhan et al., 1972; Steen, Tinker and Tarhan, 1978; Von Knorring, 1981) (table IV). However, using invasive haemodynamic monitoring and circulatory manipulation for up to 3 days after operation, one group of investigators was able to reduce this substantially (Rao, Jacobs and El-Etr, 1983). The reason postulated by the authors was the reduced use of vasopressors and greater use of vasodilators in their circulatory manipulation, but comparison was made with historical controls.

It is known that the risk of myocardial infarction related to operation persists for at least 5 or 6 days afterwards (Goldman, 1983).

It has been suggested recently that the occurrence of adverse cardiac events during anaesthesia may be predicted by dipyridamole–thallium scanning before operation. The redistribution of thallium after administration of dipyridamole is a marker for relative hypoperfusion of viable myocardium and in a series of 16 patients was shown to be a good predictor of the likelihood of ischaemic events (Boucher et al., 1985). Further large scale studies are required to elucidate the role of this technique in the preoperative evaluation of cardiac risk.

TABLE III. *Index of cardiac risk in non-cardiac procedures (Goldman et al. 1977)*

Risk factor	Points
3rd heart sound or jugular venous distension	11
M1 preceding 6 months	10
Rhythm other than sinus or premature atrial contractions	7
> 5/min ventricular extrasystoles	7
Abdominal, thoracic, aortic operation	3
Age > 70 yr	5
Important aortic stenosis	3
Emergency operation	4
Poor condition	3
Defined by any one of:	
Pa_{O_2} < 8 mm Hg (1.07 kPa)	
Pa_{CO_2} > 6.5 mm Hg (0.87 kPa)	
K^+ < 3.0 mmol $litre^{-1}$	
HCO_3 < 20 mmol $litre^{-1}$	
Creatine > 3 mmol $litre^{-1}$	
SGOT abnormal	
Chronic liver disease	

Pulmonary disease

There have been few new developments with regard to the patient at risk of pulmonary morbidity and mortality from anaesthesia and surgery. The only major change has been the acceptance for surgery of patients who would have been regarded as prohibitive risks in the past (Williams and Brenourtz, 1976). The patient at risk from pulmonary complications may be identified by preoperative screening using simple tests such as those using the Vitalograph (Appleberg, Gordon and Fatti, 1974). The application of vigorous preventative measures to such patients has been shown to reduce the complication rate by 50% (Bartlett, Gazzaniga and Geraghty (1973).

More sophisticated tests which reveal marginal lung disease are of little value in this context. Maximum breathing capacity, timed spirometry—forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC)—and arterial blood-gas analysis remain the major techniques of preoperative pulmonary evaluation (Tisi, 1979).

Patients at risk of developing pulmonary complications include the obese, smokers and those with known lung disease, especially when scheduled for upper abdominal and thoracic operations. Measures which have been shown to be useful in prophylaxis include patient education, physiotherapy and, where appropriate, pharmacological control of bronchomotor tone, infection and breathing (Stein and Cassara, 1970).

In the context of lung resection, the use of predictive volumes, regional lung function measurements (Corris, Kendrick and Gibson, 1985) and also CT scanning (especially of bullae

TABLE IV. *Studies of the risk of postoperative myocardial infarction*

Authors	Population	Incidence	Mortality	Risk factors	Factors with no risk
Topkins and Artusio (1964)	12 712			MI last 2 years	Anaesthetic agent
	Males > 50 yr	0.66%	26.5%	(25% reinfarction)	Type of surgery
				MI last 6 months	Duration of surgery
	Previous MI	6.6%	70%	(50% reinfarction)	
Tarhan et al. (1972)	32 877	0.13%	80%	Thoracic and upper abdominal operation	Type and duration of anaesthesia
	422 Previous MI	6%		MI 3–6 months (16% reinfarction) MI last 3 months (37% reinfarction)	
Steen, Tinker and Tarhan (1978)	587 All previous MI	6.1%	69%	Preoperative hypertension Intraoperative hypotension Thoracic and upper abdominal operation Duration > 3 h MI 3–6 months (11% reinfarction) MI last 3 months (27% reinfarction)	Diabetes Angina Patient age/sex Site of previous MI
Von Knorring (1981)	12 654			Preoperative hypertension	Type of surgery
	12 440 normal	0.1%		Intraoperative hypotension MI last 6 months	Type and duration of anaesthesia Diabetes
	214 "at risk" (previous MI or IHD)	17.7%			Patient age/sex
Rao, Jacobs and El-Etr (1983)	All previous MI:			CCF	
	364 (1973–76)	7.7%		Intraoperative hypertension	
	MI 0–3 months	36%		Intraoperative hypotension	
	MI 3–6 months	26%		Intraoperative tachycardia	
	733 (1977–82)	1.93%			
	MI 0–3 months	5.7%	Aggressively treated		
	MI 3–6 months	2.3%			

in different phases of ventilation) (Morgan, Strickland and Denison, 1986) are valuable in assessing postoperative ventilatory adequacy. It has been said of the prediction of risk factors in pulmonary disease: "After 23 years and dozens of spirometric studies involving thousands of patients, it is apparent that there is no spirometric number, percentage or category that will absolutely separate the operable from the inoperable patient. There are estimates of risk—guidelines to be sure—but no absolutes" (Tisi, 1979).

The elderly

It is widely agreed that preoperative assessment and the prediction of operative risk in the elderly patient is very difficult and that operative morbidity and mortality are much higher in geriatric patients, especially for emergency surgery (Cole, 1970; Cogbill, 1967; Andersen and Ostberg, 1972; Burnett and McCaffrey, 1972).

It has been found (Fowkes et al., 1982) that, in contrast to an increasing mortality after anaesthesia and surgery with advancing age, the relative mortality risk for individual concurrent disease such as ischaemic heart disease, and diabetes, is decreased. This implies that, in older age groups, co-existing disease may be less important than other risk factors in determining mortality. Del Guercio and Cohn (1980) reported a series of 148 patients older than 65 years who had been graded according to the ASA scale. None had been put in category V and in no patient had a delay in surgery been recommended in order that the patient's condition might be improved. Invasive investigation of haemodynamic and respiratory function revealed severe disease in 23% of the patients and all of this group who underwent surgery died. A further 63.5% had minor or more severe functional defects, many of which were improved before surgery by inotropic or fluid therapy. The physical status classification was found to correlate with the severity of the abnormalities found by the invasive investigation and with the operative mortality, but was unable to show what abnormalities there were and therefore offered little in terms of individual patient management.

Lorhan (1967) suggested that a much longer time for assessment of morbidity after operation (up to 6 months) is necessary in the elderly if the full implications of preoperative evaluation and therapeutic manipulations are to be revealed. However, Wilson, Strother and Allen (1967) reported that, in patients older than 60 years, intensive postoperative nursing care merely delayed inevitable deaths.

Most of the studies in the elderly have emphasized both the difficulty and the importance of thorough preoperative assessment and preparation both of the surgical condition and of any concomitant medical disease (Cole, 1968). This probably accounts for the large difference in mortality between emergency and elective operation which is widely reported in the elderly (Marshall and Fahey, 1964; Cogbill, 1967; Anderson and Ostberg, 1972).

Prediction of risk factors in general

Farrow and colleagues (1984) reported efforts to predict outcome for surgical patients. Data on 13043 operations were amassed from 108878 anaesthetic records and were analysed using a logistic regression model to determine the probability of death in hospital. In an elegant prospective pilot study using newer statistical methods based on multivariate analysis, Pedersen and colleagues (1986), examined many different operative and postoperative variables for prognostic significance. As the result of data screening, the need for artificial ventilation was taken as the most significant occurrence in the development of postoperative morbidity and mortality. A series of preoperative risk factors were subsequently evaluated for their importance with respect to this outcome. Seven factors were found and these are, listed in decreasing order of importance:

Clinical assessment—ASA > III
Cardiac failure
Cardiac risk index
Pulmonary disease
Pulmonary abnormalities confirmed by x-ray
Abnormalities in the ECG
Emergency operation

CRITICAL INCIDENT STUDIES AND DEPARTMENTAL NEAR MISS STUDIES

The critical incident technique was developed directly from studies in Aviation Psychology by the United States Army Air Forces during World War II. The nebulous reasons given for the failure of pilots in training (insufficient progress; lack of inherent flying ability; poor judgement) were replaced by examples of inadequate behaviour in different situations which could be better analysed, interpreted and applied to selection of recruits. The reasons for the failure of bombing missions and the causes of disorientation whilst flying were also investigated. These paved the way for changes in cockpit layout and training methods. Similar work was also applied to the evaluation of airline pilots (Gordon, 1950) and more recently to flight safety in the Royal Air Force (Chief of Air Staff, 1978). Critical incident techniques have also been applied with great success to subjects as diverse as job requirements (Wager and Sharon, 1951), prediction of performance in dental students (O'Donnell, 1953) and the selection of foremen and supervisors (Finkle, 1950). The reliability and validity of the critical incident technique has been confirmed by Andersson and Nilsson (1964).

The critical incident technique has been outlined in detail by Flanagan (1954) and it is worth summarizing the major features. An *incident* is defined as any observable human activity sufficiently complete in itself to permit inferences and predictions to be made. A *critical incident* is an incident occurring where the purpose or intent of the act seem clear to the observer and where its consequences are sufficiently definite as to leave little doubt concerning its effects. The technique involves collecting many such incidents in the field under investigation, analysing and interpreting them and finally making a report with recommendations.

Data may be collected in four ways, usually by investigators trained in interview and data collection techniques rather than in the area under study:

(1) *By interview*—after an explanation, the subject is asked to recall relevant events.

(2) *Group interviews*—these are less time consuming.

(3) *Questionnaires*—these are less taxing on resources.

(4) *Prospective critical incident surveys*, in which record forms are completed by trained observers as the incidents occur.

Critical Incident Techniques were applied in medicine for the first time to investigate the type and cause of errors in drug administration by nursing staff (Safren and Chapanis, 1960). Later (Sanazaro and Williamson, 1970) the technique was applied to the investigation of patient care by physicians, surgeons, paediatricians and obstetricians.

It was suggested that this type of work might be valuable in relationship to the design of anaesthetic equipment (Blum, 1971). "It is time for the anesthesiologist to realise that human perception and reaction can influence the effectiveness of his equipment, and to recognise that appropriate guidelines can assure the most fundamental form of safeguard".

Subsequently, Cooper and his colleagues (1978) adapted the critical incident technique specifically for anaesthesia. Following pilot studies, they redefined the components of the critical incident technique in the context of anaesthetic practice. A critical incident became an occurrence that could have led, if not discovered in time, or did lead, to an undesirable patient outcome ranging from increased duration of hospital stay, to death or permanent disability. Other stipulations included that the incident reported should involve either an error on the part of the anaesthetic team, or failure of anaesthetic equipment; it should occur when the patient is under anaesthetic care; and it should be described by a person who had observed or been involved in the whole occurrence. Examples included disconnections and incorrect connections in the breathing circuit, inappropriate drug administration, inadequate fluid therapy and premature tracheal extubation.

The incidents were collected and classified. Predisposing factors and events leading up to their discovery were recorded; some, from various sources as referenced, are listed in table V. These became the basis for recommending changes in certain aspects of anaesthetic practice, such as early detection of potential problems by monitoring devices or even the respositioning of monitors in more visible locations. A proportion of the critical incident work was directed towards the means by which inadvertent occurrences were discovered. An example (Newbower, Cooper and Long, 1980) may be seen in the listing of the "pivotal factors" reported in the initial discovery of breathing circuit disconnections during mechanical ventilation (table VI).

TABLE V. *Factors frequently associated with preventable anaesthesia incidents*

Failure to perform a proper checkout/history
Inadequate anaesthesia experience
Inadequate familiarity with equipment/device
Inadequate familiarity with surgical procedure
Inadequate familiarity with anaesthetic technique
Poor communication with team, lab, etc.
Lack of skilled assistance or supervision
Emergency case
Haste
Inattention/carelessness
Fatigue
Excessive dependency on other personnel
Visual field restricted
Teaching activity underway

TABLE VI. *"Pivotal Factors" reported in the initial discovery of breathing circuit disconnections during mechanical ventilation in 62 critical incidents (Newbower, Cooper and Long, 1980)*

	% of Total
Change in pulse or arterial pressure	26
Direct observation of disconnect	24
Patient colour	16
Changed performance of ventilator	13
Absent breath sounds	13
Absent chest movements	11
Poor arterial blood-gases in routine sampling	5
Change in ECG	3
Cardiac arrest	2

It became clear from this particular study that whilst the ECG was routinely monitored in the institutions studied, changes in the display were not. Also, in five of the incidents reported, the discovery of disconnection was made by another anaesthetist who came in as routine relief for lunch or coffee breaks.

The advantage of critical incident studies is that more data are available for analysis, since both near disasters and possible disasters are incorporated with actual disasters. In 95% of incidents collected by Cooper, Newbower and Long (1982) there was no mortality or long term morbidity, but subtle causes of mishap could be inferred from analysis of a large quantity of data. Furthermore, little reluctance is encountered in reporting on near disasters, compared with actual morbid events.

In a recent study, 10–30 min interviews were held by trained interviewers, carried out retrospectively but very soon after incidents (Cooper, Newbower and Kitz, 1984) and this allowed interpretation of chains of coincidences and sequences of events. It was not necessary to trace events from the anaesthetic charts—a pitfall of many retrospective mortality studies.

Retrospective analysis of data from interviewing 92 anaesthetic personnel (Cooper et al., 1982) with special emphasis on the relief of one person by another showed that, in most instances, there was a beneficial effect on patient well-being, errors being discovered on handover which had not been noticed previously. These studies have led, in some institutions, to the development of procedures providing guidance on how anaesthetists should be relieved for coffee breaks, etc.

Prospective critical incident studies have been made, with trained observers reporting on incidents as they occurred (Vaughan, Vaughan and Hagaman, 1983; Vaughan et al., 1983). These studies highlighted the importance of seemingly innocuous events and showed that nearly 50% of the patients in the operating theatre and more than 30% of patients in recovery were subjected to potential mishaps which could have led to serious consequences. In a prospective study of this type where the critical incidents collected were those related to adverse cardiac events during and after operation (Vaughan et al., 1983), preoperative clinical factors which predisposed to unfavourable outcome included: age > 50 yr; ASA III or more; major organ system disease and preoperative multiple antibiotic therapy.

It has also been observed from this type of study that, contrary to anaesthetists' opinions, the maintenance period of anaesthesia is the most dangerous in respect of *preventable* anaesthetic accidents (Cooper et al., 1978), emphasizing the need for constant vigilance.

The regular reporting and discussion of anaesthetic near disasters and their analysis (Craig and Wilson, 1981) has been found to provide a sound basis for teaching of safety aspects of anaesthetic practice.

One limitation of the critical incident technique is that reporters may be inaccurate, having embellished or misinterpreted occurrences. In addition, there is probably an unknown and unquantifiable number of errors which may or may not be involved in a chain of events resulting in morbidity or mortality, but which go unnoticed and therefore unreported.

The true incidence of error and its contribution to anaesthetic morbidity and mortality cannot be calculated from retrospective critical incident studies (Cooper, Newbower and Long, 1982). This is because the actual cause of morbid events is difficult to ascertain from data prompted from memory, particularly when multiple errors have occurred in sequence. Single, simple, isolated errors provide the most useful database. The lack of medical or anaesthetically qualified interviewers and observers may also be a source of error, although the technique had been proven with non-specialist observers in many spheres before its application to anaesthesia.

In an editorial introducing some critical incident reports, Epstein (1978) noted that the insurance industry in the U.S.A. was funding further work along the same lines.

EPIDEMIOLOGICAL STUDIES OF ANAESTHETIC MORBIDITY AND MORTALITY

Anaesthetic morbidity

Anaesthetic morbidity includes any problem (excluding death) occurring in the perioperative period. This encompasses events ranging from a minor haematoma to serious brain damage. Morbidity may be classified into three groups:

(1) *Minor morbidity.* This causes moderate distress but without prolongation of hospital stay or permanent sequelae.

(2) *Intermediate morbidity.* This causes serious distress or prolongation of hospital stay, or both, but no permanent sequelae.

(3) *Major morbidity.* This causes permanent disability or disfigurement.

Minor morbidity does not threaten the life or well-being of the patient and may be considered separately. In many instances, minor morbidity arises as a result of lack of forethought by the anaesthetist and the distress and anxiety suffered may often be reduced by explanation and reassurance. "It is evident that many of the minor sequelae of anaesthesia may be prevented by greater care in the handling of anaesthetised patients and in the techniques of anaesthesia" (Edmonds-Seal and Eve, 1962). Examples of minor morbidity are tabulated in table VII and incidences taken from a recently published study

TABLE VII. *Minor morbidity resulting from anaesthesia. (From Cohen et al. (1986))*

Nausea and vomiting: Related to operation site
Females > males
Premedication
Sore throat: Up to 70% patients
Mostly after tracheal intubation
Correlated with straining
Correlated with movement of head and neck
Headache: Up to 60%
Severe 15%
Backache
Operation site pain
Discomfort from catheters, drains, nasogastric tubes
Awareness: Dreams
Anxiety
Muscle pains (up to 100% of those receiving suxamethonium)
Shivering/spasticity: Proportional to dose of anaesthetic agent used
Drowsiness
Anorexia
Disorientation
Injection site thrombophlebitis, bruising, tenderness
Bruised/cut up
Painful neck muscles
Chipped teeth

TABLE VIII. *Incidence of minor and major anaesthetic morbidity as quoted in the study of Cohen and colleagues (1986)*

	Frequency per 10 000	
	1975–8 (n = 28637)	1979–83 (n = 34362)
No complications	9080.2	9015.3
Nausea and vomiting	512.3	554.7
Sore throat	150.9	139.1
Muscle soreness	45.4	33.9
Headache	41.6	44.0
Dental	9.1	9.9
Mechanical	51.7	42.5
Backpain	7.3	13.9
Eye problem	6.3	4.9
Upper airway	4.2	0.6
Other ventilatory	10.5	9.6
Myocardial infarction	3.8	13.7
Other cardiovascular	59	57.3
Venous	9.1	18.6
Arterial	9.4	50.9
Nerve palsy	4.2	1.8
Hepatitis	2.1	0.6
Renal	1.1	0.3
Urinary retention	10.1	4.4
Psychiatric	19.2	3.7
Awareness	12.6	10.5
Other	9.1	21.8
Major	40.6	44.5
Minor	892.6	941.5

(Cohen et al., 1986) encompassing all complications short of death are shown in table VIII.

Minor morbidity has been reviewed extensively (Edmonds-Seal and Eve, 1962; Riding, 1975). There are many studies which have evaluated the use of a particular tracheal tube (Alexopoulos and Lindholm, 1983), the presence or type of tracheal tube cuff (Jensen et al., 1982; Loeser et al., 1983), the role of premedication (Clarke, 1984; Goold, 1984) or anaesthetic technique (Stanford, Plantevin and Gilbert, 1979; Capan et al., 1983).

There have also been some conclusions of an epidemiological nature resulting from the study of minor morbidity. For example, it has been shown that personality influences both the number and type of complaints after anaesthesia (Cronin, Redfern and Utting, 1973), and that certain groups of patients are vulnerable to particular side effects. It has been reported that the incidence of nausea and vomiting (Boulton, 1955), sore throat (Wolfson, 1958), headache (Zohairy, 1969) and anxiety (Cronin, Redfern and Utting, 1973) is much higher in females.

The methods of data collection or retrieval have been found to affect the findings of surveys to a large extent (Riding, 1975); retrospective surveys of patients' records reveal far less than general questioning at interview, which in turn yields less than questions aimed specifically at the aspect of morbidity under investigation.

Assessment of minor morbidity is rarely included in large scale morbidity and mortality studies, although in a truly prospective study little additional work would be required for a large return in information.

In addition to physical changes, there may also be psychological sequelae to anaesthesia and surgery. Examples which may have long-lasting psychological effects include awareness and postoperative pain. It is interesting that the medico–legal implications of awareness are currently assuming great importance in the U.K., in contrast to the lack of adequate postoperative pain relief. In both instances, the anaesthetist has to balance the side effects of obtunded protective reflexes and depression of vital centres against the morbidity resulting from insufficient analgesia and anaesthesia.

The cases reported to the Medical Defence Organisations have been used as a database in the U.K. for investigating anaesthetic mortality and morbidity (Wylie, 1975; Utting, Gray and Shelley, 1979; Gray, 1985), although it would

TABLE IX. *Anaesthetic morbidity reported to the Medical Defence Union, 1970–1977 (Utting, Gray and Shelley, 1979)*

Damage to teeth		127
Neurological		
Cerebral	71	108
Spinal cord	8	
Peripheral nerves	29	
Superficial thrombosis/thrombophlebitis		32
Extradural foreign bodies		27
Awareness		11
Extravasation of injected drugs		8
Pneumothorax		5
Burns		3

seem reasonable to suppose that these data must be highly selected. However, it has been suggested that they probably contain the most accurate information on the incidence of severe neurological damage following anaesthesia (Gray, 1985). The commonest anaesthetic accident reported between 1970 and 1977 (Utting, Gray and Shelley, 1979) was death, the next most common being damage to the teeth (table IX).

Anaesthetic mortality and complications

Epidemiological studies vary widely in their nature and objectives. Many of the earlier reports comprised simple description of anaesthetic deaths, with the intent of defining aetiology (table X).

In other studies deaths and complications are presented against the total number of surgical operations during the study period with, perhaps, details of anaesthetic and surgical practice. These studies vary in magnitude from a report of the deaths in the practice of a single anaesthetist to the incorporation and analysis of data on mortality from more than a million operations in many centres (table XI).

The difference in design, database and interpretation of these studies mitigate against firm conclusions, but clear trends have emerged:

(1) In the more recent studies, the incidence of anaesthetic mortality does not vary widely (table XII).

(2) The factors which have contributed to

TABLE X. *Reports of anaesthetic deaths and cardiac arrests*

Authors	Year	Report
Macintosh	1948	Anecdotal reports of anaesthetic deaths
Edwards et al.	1956	1000 Deaths reported over 5.5 years in the year U.K.
Stephenson, Reid and Hinton	1953	1200 Cardiac arrests—worldwide
Boba and Landmesser	1961	61 Cardiac arrests over 3 years—Albany Hospital, New York
Taylor, Larson and Prestwich	1976	41 Cardiac arrests from insurance company records 1956–71

TABLE XI. *Reported incidences of anaesthetic and surgical mortality*

Study	Location	No. operations/ anaesthetics	No. deaths
Lunn and Mushin (1982)	Five regions in the U.K.	1 147 362	3736
Beecher and Todd (1954)	Ten university hospitals, U.S.A.	599 548	7977
Hovi-Viander (1980)	100 Finnish hospitals	338 934	626
Harrison (1978)	Groote Schuur Hospital, Cape Town, R.S.A.	240 483	2442
Turnbull, Fancourt-Smith and Banting (1980)	Vancouver General Hospital, Canada	195 232	423
Tiret and Hatton (1986)	460 Private and public Hospitals, France	198 103	67 (16 coma)
Memery (1965)	Springfield and Weston Maternity Hospital, Massachussetts, U.S.A.	114 866	179
Marx, Matteo and Orkin (1973)	Bronx Municipal Hospital Center N.Y., U.S.A.	34 145	645

TABLE XII. *Findings of more recent anaesthetic mortality studies. D = Total anaesthetic/surgical mortality; A = anaesthetic associated deaths; P = preventable anaesthetic deaths; T = totally attributable to anaesthesia*

Study	Details	Deaths/ 10 000	Category
Tiret and Hatton	460 Public and private hospitals	4.2	D
(1986)	198 103 Anaesthetics	1.26	A
	Prospective within 24 h		
Lunn and Mushin	Five regions U.K.	62.5	D
(1982)	1 147 362 Anaesthetics	5.9	A
	Within 6 days	1	T
Hovi-Viander	100 Finnish hospitals	18	D
(1980)	338 934 Anaesthetics	2	A
	Within 3 days		
Turnbull, Fancourt-Smith	Vancouver General	22	D
and Banting (1980)	195 232 Anaesthetics	2	P
	Within 48 h		
Harrison (1978)	Groote Schuur Hospital	100	D
	240 483 Operations	22	A
	Within 24 h	2	P
Anaesthetics Mortality	All hospitals in S. Australia	5	A
Committee (1976)	465 000 Anaesthetics	0.8	T

TABLE XIII. *Factors commonly reported as contributing to anaesthetic mortality*

- Before operation
  - Inadequate preanaesthetic assessment
  - Uncorrected hypovolaemia
- During operation
  - Pulmonary aspiration
  - Inadequate monitoring
  - Problems with tracheal intubation
  - Inexperience/Lack of supervision of junior/Inappropriate technique
  - Hypoxic gas mixture
- After operation
  - Inadequate supervision of patient
  - Ventilatory failure—opioids, myoneural blockade

TABLE XIV. *Common recommendations which have emerged from anaesthetic mortality studies*

- Careful attention to preoperative assessment
- Full resuscitation before operation, with central venous pressure measurement where appropriate
- Completion of a readable complete anaesthetic record
- More qualified anaesthetists
- Better monitoring facilities/Use of monitoring equipment
- More recovery rooms

anaesthetic mortality have remained relatively constant over the years, although their relative importance may differ according to the data of different studies (table XIII).

(3) The conclusions and recommendations which have emerged from large scale studies are similar and these are shown in table XIV.

Problems in Epidemiological Studies

Further studies of anaesthetic mortality and morbidity are required to establish a worldwide database for monitoring anaesthetic standards, since the existing database is too narrow and many studies exhibited problems which require resolution. These problems may be considered under the following headings:

Lack of uniformity: Population
  Definition
  Time span
  Changing practice of anaesthesia
Lack of objectivity: Blame
  Errors
Study design: Methods of data collection:
  Prospective/retrospective
  Voluntary/compulsory
 Data processing:
  Checking
  Anonymity
  Classification of outcome
 Feedback

LACK OF UNIFORMITY

A major criticism of epidemiological studies of morbid and fatal events associated with anaesthesia to date is their lack of uniformity. This produces difficulty in comparing different studies.

Population (see table XI). Few studies have been undertaken on populations which bear a resemblance to the area of study as a whole. Many are drawn from one hospital or a group of hospitals served by the same department. Thus patient populations in the studies of teaching hospitals (Beecher and Todd, 1954; Harrison, 1968, 1978) probably differ markedly from those of smaller private practice hospitals (Memery, 1965).

Lunn and colleagues (Lunn and Mushin, 1982; Lunn, Hunter and Scott, 1983) collected reports from all hospitals in the National Health Service in five regions of the U.K., but no private establishments were included. In contrast, Tiret and Hatton (1986) collected data from 460 institutions in France comprising private hospitals, and teaching and non-teaching public institutions. The data were collected over two intervals, the duration of which was chosen according to the size of the establishment. The two intervals were separated by 6 months to take account of seasonal variation. This elegant design is unique.

Definition. There is no uniformity in defining events included in the large scale anaesthetic morbidity and mortality studies since the aims of investigators vary. Some categorize all deaths around the time of operation and surgery because they are interested in surgical and anaesthetic contributions to mortality (Lunn and Mushin, 1982; Lunn, Hunter and Scott, 1983). A number of investigators have limited themselves to those deaths which are thought to have been the result of anaesthesia, and others include all cardiac arrests in the operating and recovery rooms (Stephenson, Reid and Hinton, 1953; Boba and Landmesser, 1961). One notable exception to these criteria is the study of Cohen and associates (1986) who have performed an extensive survey, of all complications short of death in their institution over a number of years.

To compound this problem, the definition of what has been included or excluded is often missing: "We cannot provide individual protocols because of lack of space" (Dripps, Lamont and Eckenhoff, 1961). The absence of a clearly defined procedure limits the value of this type of study and may be the reason for the widely differing results obtained in the past.

Anaesthetic deaths have been defined as the death of a patient under or before recovery from an anaesthetic or arising from any incident during anaesthesia (Clifton and Hotten, 1963). Other groups investigating anaesthetic mortality have incorporated deaths in the operating theatre alone (Waters and Gillespie, 1944). In one study (Phillips et al., 1960) two deaths were included as being associated with anaesthesia where no anaesthetic had been given—it was considered by the investigators that, had the anaesthetist become involved and given an anaesthetic after adequate resuscitation, a more favourable outcome would have ensued.

There are two possible approaches which might be recommended. Since morbid events are related to the interaction of anaesthetic drugs and procedures, surgical events and the patient's disease, it has been suggested that the analysis of morbidity and mortality data following standard operations in ASA I and II patients may reveal valuable information which should be easy to interpret. The other approach is to collect information on all deaths occurring in the operating theatre and for a given time after operation and then, using set guidelines, elucidate the relative contributions of anaesthesia, surgery and intrinsic disease.

Discussion at an international symposium on preventable anaesthetic morbidity and mortality in 1984 resulted in a working definition for anaesthetic mortality: "A death which occurred before recovery from the effects of a drug or drugs given to relieve the pain of a condition or arising from an incident which occurred while the drugs were effective" (Lunn, 1985a). As may be seen, the terms anaesthesia, anaesthetic, anaesthetist and operation are not mentioned. Virtually all deaths in hospital would be included by this definition, resulting in an enormous database.

The phraseology used in questionnaires may influence the number of deaths reported. In one study (Ruth, 1945) it was suggested that deaths were not being reported to the "Anaesthetic Mortality Commission" which had been set up to investigate deaths resulting from anaesthesia: "From our activities it was evident that a material number of fatalities were being classified as sudden deaths from other causes". The criteria for inclusion in the study were subsequently changed to all fatalities, whatever the cause, on the first 2 days following surgery. At the same time, the title of the investigating body was changed to

TABLE XV. *Time span of anaesthetic morbidity and mortality studies*

Study	Time span
Dealy (1943)	Death at operation or a few minutes after (excluding local and i.v. anaesthetics)
Waters and Gillespie (1944)	Death in the operating room
Beecher and Todd (1954)	All deaths on the surgical services
Hingson, Holden and Barnes (1956)	Death within 24 h
Dornette and Orth (1956)	Deaths in the operating room or after failure to regain consciousness
Clifton and Hotten (1963)	Any death under, attributable to or without return of consciousness after, anaesthesia
Harrison (1968, 1978)	Death within 24 h
Marx, Matteo and Orkin (1973)	Death within 5 days
Anaesthetics Mortality Committee (1976)	Death within 24 h
Hovi-Viander (1980)	Death within 3 days
Lunn and Mushin (1982)	Death within 6 days
Tiret and Hatton (1986)	Complications within 24 h

"Anaesthetic Study Commission". This resulted in a considerable increase in reporting.

Time span. There is considerable variation between different studies in the interval between surgery and death (table XV).

In many instances, this seems to be the result of an arbitrary choice, possibly relating to the ease with which the data may be collected. In some studies, only deaths in the operating theatre were incorporated, whilst in others periods from 24 h to 30 days after surgery have been advocated. Two studies (Fowkes et al., 1982; Farrow et al., 1984) from Cardiff incorporated all deaths occurring during the hospital stay although, for the elderly patient, it has been suggested (Lorhan, 1967) that it would be more realistic to study all deaths within 6 months of operation.

In the prospective study reported recently from France (Tiret and Hatton, 1986) a 24-h period was accepted, since it was felt that few deaths would be missed because all complications were recorded at 24 h and it is rare for a death to occur without early premonitory signs.

The Lunn and Mushin enquiry (1982) and its follow-up (Lunn, Hunter and Scott, 1983) covered a period of 6 days after operation. This was validated by earlier epidemiological studies undertaken in Cardiff (Mushin, Campbell and Shang, 1967).

TABLE XVI. *Response rates in the U.K. and French studies*

Study	Response rate	Study period	Deaths (and coma)
Lunn and Mushin (1982)	61%	6 days	1/10 000
Tiret and Hatton (1986)	87%	24 h	1/8000

A comparison of the death rates between the studies of Lunn and Mushin (1982) and of Tiret and Hatton (1986) reveals striking similarities, especially if those patients in coma in the French study are also included. The differences may be explained by the different response rates (table XVI).

The most recent study presently in progress in the U.K.—the Confidential Enquiry into Perioperative Mortality (CEPOD)—is the first British investigation to include surgical mortality and, for this reason, the study period has been extended to 30 days after operation (Lunn, 1985b).

Changing practice of anaesthesia. During the 5 years of the study by Beecher and Todd (1954) there were considerable changes in anaesthetic practice. In the U.K. study, Mushin, Campbell and Shang (1967) reported an increase in the use of halothane from 5% to 80% of anaesthetics between 1958 and 1964, the period under scrutiny. Such rapid change in anaesthetic practice renders difficult direct comparisons of different studies.

LACK OF OBJECTIVITY

Blame. The element of blame in reports is often denied by the investigators, but is easy to find. Lunn and Mushin (1982) lamented the refusal of individuals to participate in their study and continued:

"Perhaps it is inevitable in a voluntary study and in the current climate of suspicion that in any review of clinical practice, which might appear—quite unjustifiably—to involve an element of blame such instances of lack of co-operation occur". This sentence appears in the paragraph below the account of an anaesthetic death in a patient who was jaundiced, diabetic and had sustained a myocardial infarction 6 months previously. During the operation treatment comprised administration of dextrose–saline 300 ml and the patient died 36 h later. The report states "Thus our assessors could discern something not only about the anaesthetist, but also about the quality of anaesthetic care given to this particular patient". It is notable that in the follow up study (Lunn, Hunter and Scott, 1983) the response rate of completed questionnaires was considerably reduced.

Errors. In mortality studies, deaths are classified according to their cause: in the past there has often been too much emphasis on mistakes. Boba and Landmesser (1961) classified all cases of cardiac arrest in the operating room and in recovery; they describe "contributory and causative errors of omission and commission for which the anaesthetist must assume responsibility". In another study (Holland, 1970), if the anaesthetist was found to be partly or wholly responsible, it was then decided whether it was because of errors of judgement, of management or of technique and, finally, the number of errors per anaesthetist was computed—specialists having 3.5 errors per death and non-specialists nearly 5.

DESIGN OF STUDIES

Methods of data collection

The methods of data collection are not standardized between different studies. At the International Symposium on Preventable Anaesthetic Morbidity and Mortality (Keats and Siker, 1985) it was reported that "There was little enthusiasm for undertaking new large scale studies in any format used in the past".

Prospective or retrospective. A true prospective study gathers information before a complication ensues. Because morbid events occur so rarely, this type of work produces a vast amount of data, the majority of which are not used. An example of a prospective study is that of Tiret and Hatton (1986), in which personnel and resources could neither cope with nor vouch for the accuracy of data collected for a period of more than 24 h. This may be a problem of the prospective approach (unless very large resources are available to enable extension of the time of study) because major morbidity may occur outside this period (e.g. myocardial infarction).

The advantages of collecting the data in a truly prospective manner include the ease with which both major and minor morbidity may be incorporated to the database. The population at risk is known, so that the true incidences of morbidity and mortality can be calculated and correlated with, for example, the anaesthetic practice of different grades of anaesthetist.

With prospective studies, there is no reliance on badly written, scanty records, or poor memory, and little opportunity for the collection of biased samples as occurred in the National Halothane Study (Bunker, 1969), in which institutions were chosen which had already reported cases of jaundice after halothane exposure, so that these could be included.

A prospective study comparing four anaesthetic regimens in 20000 patients is currently being undertaken in Canada and the U.S.A.

Voluntary or compulsory. Most large scale studies rely on the voluntary co-operation of anaesthetists. The Lunn and Mushin (1982) report in the U.K. relied on the completion and return of a questionnaire sent out in response to the report of an anaesthetic death by an observer in the region. The voluntary aspect of this methodology has been strongly criticized (Flowerdew, 1983): "Surely such a system must not be voluntary it must be compulsory. The careless or inept anaesthetist is most unlikely voluntarily to submit himself for review. Furthermore, if there is not even a threat of discovery why bother to change? If an anaesthetist can repeatedly make careless mistakes by inept judgements and avoid being called to task simply by electing not to report these incidents to a voluntary review panel, then the public whom the system is designed to protect will perceive it to be merely window dressing".

Substance was lent to these statements when Devlin and Lunn (1986) reported that a registrar refused to fill in the questionnaire as part of CEPOD because it was not in his job description. This consideration would not be problem in a prospective study once initial permission had been granted for the study to take place. "It is to be emphasised that there is nothing voluntary or selective about the reporting of deaths once an institution with its team has agreed to participate" (Beecher and Todd, 1954).

In a recently published work investigating all complications short of death (Cohen et al., 1986), although participation by the anaesthetic staff was not compulsory, it was encouraged by the fact that the billing form was an essential part of the anaesthetic follow-up form.

Data processing

Checking data. A system of checking data is essential in order that its accuracy may be verified. The Lunn and Mushin (1982) enquiry used the data collected by the DHSS in the "Hospitals Activity Analysis" (HAA), as will CEPOD. The HAA was criticized (Lunn and Mushin, 1982; Lunn, Hunter and Scott, 1983) because, in some regions, data were processed a long time after the events and also, because non-medically qualified clerks were involved, it was subject to some inaccuracies.

In Cardiff, epidemiological data concerning anaesthesia, surgery and hospital mortality have been collected since 1954. The quality control of earlier work had been achieved by the checking of randomly selected data cards, taking advantage of a youth scheme set up at the time. Since then, random computer checks are made, checking in addition for errors such as the recording of male operation on female patients.

During the collection of their data concerning all complications short of death (Cohen et al., 1986), quality control was achieved by a nurse employed full-time to see patients after their operation and to check the follow-up forms filled in by the anaesthetists (Burnham and Craig, 1980).

Anonymity of doctors and patients is usually assured by some processing of the data before analysis and reporting. This is very important, for medico-legal reasons. In some instances, medical defence organizations have been closely involved with this step (Lunn and Mushin, 1982). It allows participation without fear of medico-legal repercussions. One possible drawback is that rechecking data in the light of new advances is made more difficult or even impossible.

The method of processing data reflects the aims of the investigators. Occasionally, only numerical data are reported. In the majority, some educational or preventative role is intended. In some instances, the authors asked the institution involved for their opinions. Beecher and Todd (1954) stated "We accepted the conclusion arrived at in the institution: certainly we had not the right to change the diagnoses or to alter conclusions arrived at by the participants". More often the individual or the committee undertaking the study also decides upon the contribution to death or complication produced by intrinsic disease of the patient, anaesthesia and surgery. In many studies (Holland, 1970; Hovi-Viander, 1980; Tiret and Hatton, 1986) the opinions of those involved may have been taken into account, but those of the investigators were usually final. This approach has been criticized: "In only two studies were the judges not completely omniscient in determining the cause of death" (Keats, 1979).

Classification of outcome can be approached in many different ways—these were recently discussed and tabulated (Keats and Siker, 1985) under five headings: First, as an occurrence causing a cascade of events resulting in a complication, the interventions necessary to halt the process requiring classification; second, undesirable outcomes being defined in terms of the increase in the cost of therapy and duration of stay over that expected; third, a simple classification in terms of the organ affected; fourth, the anaesthesia management area affected: airway, circulation, drugs; and finally, in terms of a list of adverse anaesthetic occurrences.

It was acknowledged in the ensuing discussion that there was often inability to document the relationship between anaesthesia and undesirable outcome, except in a few instances where there was a blatant error such as unnoticed disconnection, oesophageal intubation or incorrect administration of a drug. In most mortality studies, deaths are classified according to what is believed to be their cause and also whether or not they were deemed inevitable or avoidable.

Feedback

Beecher and Todd (1954) emphasized the importance of regular feedback to the participants of a mortality study. They found, in many institutions, considerable ignorance of the total death rate arising from anaesthesia. The Special Committee investigating deaths under anaesthesia in Australia (Holland, 1970) disclosed that, in approximately 50% of instances, the opinion of the anaesthetist involved was at variance with its own, although specialists were more likely to agree than trainees and non-specialists.

In an Editorial introducing CEPOD, Lunn

(1985b) indicated that, because of its anticipated large numbers, it would be possible to arrange for feedback of the Committee's opinions and still preserve anonymity. This was to be undertaken on request to those who desired it. It is interesting that, in the preliminary results (Devlin and Lunn, 1986), a mere 20 requests had been made for this service from a possible total of 1300.

SUMMARY

In the past two to three decades, advancing knowledge in the areas of physiology, pharmacology and scientific technology have allowed diversification from the purely technical aspects of administration of anaesthesia towards more accurate assessment of outcome for the individual in terms of both anaesthetic-induced morbidity and mortality. In addition, elucidation of the aetiology of the morbidity and mortality produced by anaesthesia, as opposed to that from surgery or concomitant medical or surgical disease processes, is assuming increased importance as a result of the expansion in medical litigation, where anaesthetists find themselves amongst the higher risk specialties in medicine.

The morbidity produced by anaesthesia is relatively easy to define for specific populations, but the prediction of risk in an isolated individual remains elusive. For example, there are many studies indicating the incidence of postoperative myocardial infarction following surgical procedures in defined groups; but for the individual patient, more sophisticated risk assessments have so far failed to predict more accurately than the well-established ASA grading system. Nonetheless, it is expected that in future, studies in this area will permit increased precision in the assessment of risk, thereby permitting better consideration by both surgeon and patient of the options available regarding surgical and non-surgical therapy.

Increasing emphasis on the safer administration of anaesthesia has been greatly aided by the use of the critical incident technique. By assessing near-misses in addition to existing morbidity and mortality, the technique increases the size and extent of the database, and by removal of the reticence inherent in an anaesthetist's confession of his mistakes, it increases the reporting of potential mishaps. Amongst the useful findings to have emerged from such studies is the previously unforeseen and unsuspected observation that the most dangerous period of anaesthesia is not during induction and recovery, but during the maintenance period. However, perhaps one of the more valuable aspects of this type of methodology is its potential use in quality control and audit within departments.

There are undoubted problems and universally acknowledged difficulties in epidemiological research into anaesthetic mortality. Comparison of data between studies is rendered difficult owing to variations in procedure, including its prospective or retrospective nature, the definition of death, the perioperative time period studied, and the patient and hospital populations encompassed. In addition, causes of death are largely putative and may involve speculation on errors, thereby containing some elements of blame or fault. Nonetheless, it seems likely, largely because of the similarity between the results of different studies from the U.S.A., the U.K., France and Australia, that mortality related to anaesthesia lies between 1:5000 and 1:10000 operations. However, anaesthesia is rarely a therapeutic manoeuvre in itself and no study to date has dissected the relative surgical contribution away from that of anaesthesia. Hopefully, the large scale confidential enquiry into all perioperative deaths (CEPOD) which was initiated between the Associations of Anaesthetists and of Surgeons of Great Britain and Ireland in 1985 will cast further light on this aspect of the subject.

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ANAESTHETIC MORTALITY IN NEW SOUTH WALES

R. HOLLAND

Since 1960, a Ministerial Committee has investigated deaths occurring in relation to anaesthesia in New South Wales, Australia. The Committee, comprising six anaesthetists (one of whom is Chairman), three surgeons, an obstetrician, a general practitioner and a medical administrator, has functioned continuously except for a 3-year period from mid-1980 to mid-1983. This interruption resulted from a temporary inability to guarantee confidentiality, since restored by legislation.

The Coroner's Act, and the Births, Deaths and Marriages Act of New South Wales (N.S.W.) preclude the issue of a death certificate for any patient who dies, *inter alia*, "whilst under, as a result of, or within 24 hours of an anaesthetic..." and require that such deaths be reported to the Coroner.

The Committee enjoys access to the Coronial notifications which result, and is therefore able to contact all anaesthetists involved in cases where death occurs under the above circumstances. Information is solicited via a structured questionnaire, preceded by a simple inquiry so as to ascertain whether the death is one which fits the Committee's definition, *viz.* "...the death of a patient under, or prior to complete recovery from; or arising out of any incident during the anaesthetic."

Despite the voluntary nature of this inquiry, the Committee enjoys a response rate of over 90% (table I). This high level of co-operation is dependent on the Committee's guarantees of discretion and its unbroken record of confidentiality.

Deaths which fail to comply with the Committee's definition are not pursued further. Many of these patients had received only local infiltration anaesthesia for minor procedures during the 24 h preceding their deaths. Such exclusions amount to nearly half of the Coronial source material (table II).

Assessment of the remainder is accomplished by circulation to Committee members of all data, *minus* any identifiable material, 2 weeks before each monthly meeting. At the meeting the

TABLE I. *Rate of response to Committee's questionnaire*

	1960–69	1970–80	1983–85	Total
Cases notified	1910	2507	845	5262
Information received	1755	2346	816	4917
(response rate)	(92%)	(94%)	(96%)	(93.4%)
Information unobtainable	155	161	29	345

TABLE II. *Exclusions from further analysis by the Committee*

	1960–69	1970–80	1983–85	Total
Cases for which information is received	1755	2346	816	4917
Excluded	794 (45%)	1198 (51%)	362 (44%)	2354 (48%)
For further assessment	961	1148	454	2563

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TABLE III. *Classification of causes of mortality*

Category	Cause
I	Where it is reasonably certain that death was caused by the anaesthetic agent or technique of administration, or in other ways coming directly within the anaesthetist's province.
II	Similar cases, but in which there is some element of doubt as to whether the agent or technique was entirely responsible for the fatal result.
III	Cases in which the patient's death was caused by both the anaesthetic and surgical technique.
IV	Deaths entirely attributable to surgical technique.
V	Inevitable deaths, e.g. cases of severe general peritonitis, but in which anaesthetic and surgical techniques were apparently satisfactory.
VI	Fortuitous deaths, e.g. as a result of pulmonary embolism.
VII	Cases which cannot be assessed, despite considerable data.
VIII	Cases on which an opinion could not be formed on account of inadequacy of data.

Committee is required to classify each case into one of eight categories, as first used by Edwards and colleagues (1956) (table III).

The first three of these categories are those in which anaesthesia has played a part in causing the patient's death. Of all deaths classified, these categories form approximately 25%; that is, in those deaths which meet the Committee's definition, 25% are attributable partly or wholly to anaesthesia. However, this overall percentage for the whole series conceals a decline in the proportion of anaesthesia-attributable mortality since the Committee began its activities. The proportion in 1983–85 is now 12.2% of classified cases, and 6.4% of notifications (table IV).

Deaths not falling into one of the anaesthesia-attributable categories are for the most part "inevitable" deaths, and the proportion of these is increasing. Approximately the same number of classified deaths are attributable to surgery as to anaesthesia, bearing in mind that there is an overlap in categories III and IV (table V). Here again, however, a trend is evident as the study has progressed, and it would now appear that deaths occurring before recovery from anaesthesia are more likely to result from surgery than from anaesthesia.

Another interesting development, which presumably reflects increasing expertise and confidence in the Committee, in addition to improved reporting by respondents, is the decline in non-assessable cases from 7.6% to 1.7%.

Despite rigorous criteria calling for autopsy findings or unequivocal clinical evidence at the

TABLE IV. *Cases classified as those in which anaesthesia has played a role (categories I, II and III). *At the time of writing (September, 1986), 48 deaths occurring during late 1985 still awaited classification*

	1960–69	1970–80	1983–85	Total
Notifications	1910	2507	845	5262
Classified cases	961	1149	406*	2516
Categories I, II and III	335	239	50	624
(% of classified cases)	(35%)	(21%)	(12.2%)	(25%)

TABLE V. *Classification of all deaths reported to the Committee*

Category	1960–69	1970–80	1983–85	Total
I, II and III (Anaesthesia-attributable)	335	239	50	624
III and IV (Surgery-attributable)	292	342	91	725
IV (Surgery only)	212	253	78	543
V (Inevitable)	313	550	259	1122
VI (Fortuitous)	28	51	12	91
VII and VIII (Non-assessable)	73	56	7	136
Totals	961	1149	406	2516

TABLE VI. *Categories of errors of management, used by the Committee in classifying deaths*

Category	Error
1	Inadequate preparation for anaesthesia or surgery, or both.
2	Wrong choice of agent or technique.
3	Overdose.
4	Inhalation of gastric content.
5	Inadequate intraoperative resuscitation.
6	Hypoxic gas mixture.
7	Inadequate ventilation during anaesthesia.
8	Inadequate monitoring.
9	Technical mishap.
10	Inadequate crisis management.
11	Inadequate antagonism of neuromuscular blockade.
12	Inadequate postoperative management.

time of crisis, fortuitous deaths now account for one-fifth as many cases as in categories I–III, compared with fewer than one-tenth 15 years earlier.

In addition to classifying cases, whenever a death is placed in one of the anaesthesia-attributable categories, the Committee is obliged to state which of 12 errors of management has been present (table VI). The arrangement of these errors in table VI is chronological with respect to the anaesthesia, and bears no relationship to the frequency of their occurrence. Some discussion of the ways in which these errors are identified follows.

Inadequate preparation. The commonest circumstance in which the Committee identifies this error is the emergency in which insufficient time or effort goes into resuscitating the patient to a state in which he or she can survive the anaesthetic. Sometimes this is straightforward failure to replace blood volume (as in, say, the post-tonsillectomy bleed). More often it represents failure to appreciate the degree of dehydration and electrolyte disturbance present in a patient who has been sick for days with an obstructive or inflammatory intra-abdominal lesion.

More seldom, an elective case is insufficiently prepared or investigated, and serious pathology is not detected which alters the response of the patient to anaesthesia. An example is chronic renal dysfunction in the elderly. Occasionally, a patient who is suffering from frank heart failure is submitted prematurely to anaesthesia for elective surgery, with inadequate or no prior attempts to improve cardiac status.

Wrong choice. This subjective judgement by the Committee has been challenged on the grounds that, whatever the technique or agent, if it had been correctly administered, the patient would have survived. The Committee does not support this view, and identifies this error if there was a feasible method, within the capability of the anaesthetist, safer than that chosen. Classic examples include: choice of an agent dependent on kidney excretion in a patient with (known) chronic renal failure; general anaesthesia chosen by an operator anaesthetist for a minor peripheral procedure (toenail removal); mid-spinal anaesthesia for intestinal obstruction in a patient with cardiac compromise; spontaneous ventilation techniques in patients with postural handicaps to ventilation.

Overdose. This needs little explanation, but is relevant to the entire range of drugs used in anaesthesia. Perhaps the commonest misuse is of the i.v. barbiturate, but neuromuscular blocking drugs, opioids (especially after operation), volatile agents and even drugs used in resuscitation such as bicarbonate have all been identified. Local anaesthetic agents in overdosage account for very few deaths, although blocks which ascend beyond the intended level are more frequent. The latter are *not* classified as overdosage.

Inhalation of gastric contents continues to occur, although its incidence now is as likely to be postoperative as at induction. Obstetric disasters as a result of this accident were very common in the early years of the study, but a welcome decline is now evident.

Inadequate intra-operative resuscitation. Again, this error is self-evident. Nevertheless, it is occasionally surprising to the Committee that, in the presence of bleeding and a decreasing arterial pressure, replacement is deferred or dilatory. A recent phenomenon is a tendency to delay administration of vasopressors in favour of large crystalloid fluid loads in patients with hypotension following subarachnoid or extradural blocks, with unfortunate consequences.

Hypoxic mixtures resulting from incorrect flowmeter settings, failed oxygen supplies or cross-connections have disappeared, and this error is of largely historical significance. There appears to be a much better appreciation of the uptake and distribution of gases and the performance of breathing systems than was once the case.

Inadequate ventilation. This may arise from spontaneous ventilation through a tracheal tube of

TABLE VII. *Errors of management: numbers, and rank order of frequency*

	1960–69		1970–80		1983–85		Whole series	
Error	No.	Rank	No.	Rank	No.	Rank	No.	Rank
(1) Inadequate preparation	102	3 =	93	1	23	1	218	1
(2) Wrong choice	120	2	65	3	13	4	198	2
(3) Overdose	127	1	34	7	14	3	175	4
(4) Inhalation	41	9	18	11	1	9 =	60	10
(5) Inadequate resuscitation	63	7	49	4	6	5 =	118	6
(6) Hypoxic mixture	14	12	0	—	0	—	14	12
(7) Inadequate ventilation	68	5 =	21	9	1	9 =	90	7
(8) Inadequate monitoring	22	11	19	10	6	5 =	47	11
(9) Technical mishap	25	10	40	6	1	9 =	66	9
(10) Inadequate crisis management	102	3 =	80	2	4	8	186	3
(11) Inadequate reversal	52	8	22	8	5	7	79	8
(12) Inadequate postop. management	68	5 =	43	5	16	2	127	5
Total errors	804		484		90		1378	
Errors per patient	2.4		2.0		1.8		2.2	

inadequate calibre; or failure to support ventilation when the patient's bodily habitus, posture, or both, impose serious ventilatory handicaps during anaesthesia.

Inadequate monitoring. This error has been judged to occur according to the standards of the time and place in which the anaesthetic was given. In many of the venues, even including major hospitals in 1960, facilities for electronic monitoring were not available in every operating room. Nowadays, on the other hand, disconnect alarms are virtually standard equipment wherever mechanical ventilators are present. The Committee looks much more critically for this error now than it once did, but it is not as frequent as some authorities suggest (Cooper, Newbower and Kitz, 1984). Usually the anaesthetist is only too aware of the condition of his patient, which has resulted from an earlier incorrect decision which no amount of monitoring could have prevented.

Technical mishap (Holland, 1984). It is to the credit of the respondents, and a tribute to the confidentiality of the Committee, that technical disasters are reported so frankly. Misplaced tracheal tubes and circuit disconnections or misconnections head the list of these. Naturally, monitoring errors are sometimes (but not always) associated. Overall, this error is increasing as a *proportion* of anaesthesia catastrophe, but this is a result of reduction in the errors from ignorance. In view of the devastating medico–legal consequences of technical mishap, which in our experience always incorporates a substantial human element, anaesthetists are obviously obliged to pay particular attention to its prevention.

Inadequate crisis management. This ranges over inappropriate use of drugs, in either excessive or insufficient quantities, together with failure to use appropriate physical methods, for example control of ventilation. Although the general application of cardiopulmonary resuscitation has improved, it is somewhat disappointing that anaesthetists supposedly expert in the field of physiological homeostasis do not always react efficiently when an anaesthetized patient begins to decompensate.

Inadequate antagonism of neuromuscular blockade. This is identified less often now, but at one time was widespread. It may be that the Committee's strong recommendations for adequate doses of anticholinesterases, after a sufficient interval since administration of the blocking drug, have had some effect on the practice of N.S.W. anaesthetists (Holland, 1970).

Inadequate post-anaesthetic management. The Committee identifies this error when the patient

TABLE VIII. *Deaths attributable to anaesthesia, and those in which no error was committed by the anaesthetist*

	1960–69	1970–80	1983–85
All anaesthesia-attributable deaths	335	239	50
No errors	10 (2.8%)	12 (5%)	5 (10%)

dies at a time when the anaesthetist is still responsible for his or her welfare, and when steps have not been taken to provide adequate care. It is a matter of concern to the Committee that patients may be well-resuscitated and expertly anaesthetized, yet left to take their chances after operation in less than optimum surroundings. It seems pointless to go to the trouble of performing a difficult operation on a seriously ill patient, and not follow through with suitable postoperative care.

Table VII shows the variations in the incidence of these errors of management over the years of the study.

Occasionally, although the Committee is obliged to classify a case in one of the anaesthesia-attributable categories, it is unable to identify an error on the part of the anaesthetist. One such situation occurs when the patient is an unsuspected malignant hyperpyrexial subject, and despite the anaesthetist's best efforts (judged by the standards of the time), the patient does not survive. There are very few of these "error-less deaths" as can be seen from table VIII, but the proportion is increasing.

Certain errors have declined in importance or disappeared (overdosage, hypoxic mixture); others remain fairly static in incidence (inadequate crisis management, inadequate postoperative management), whilst a few have increased in significance (inadequate preparation, technical mishap).

In the Committee's earlier deliberations, no judgements were made as to the competence or experience of the anaesthetist. As a prospective study, attempts are now being made to evaluate these qualities, but the numbers are as yet too few for any conclusions to be drawn or data presented.

Anaesthetists

It is, of course, a matter of great interest and importance to record the status of the anaesthetists at whose hands these deaths occurred. It is here that great changes have occurred in the years of the survey (table IX).

Specialists are defined as persons possessing a Fellowship of the Faculty of Anaesthetists, R.A.C.S., or a similar qualification recognized by the National Specialists Qualifications Advisory Committee of the Commonwealth Department of Health (N.S.Q.A.C.). Registrars are persons in recognized training positions; residents are junior Hospital staff in non-training positions. All other medical graduates acting as anaesthetists are non-specialists.

In analysing these data, it is important to appreciate that the denominators are not precisely known. It is known that the total number of anaesthetics administered per year in N.S.W. exceeds 500000 (G. McCleary, 1986; unpublished data), but the proportion of these administered by practitioners from each category is unclear. Some approximations are possible. For instance, the Faculty of Anaesthetists has 92 registered trainees in N.S.W., and conducts periodic "work surveys" to check on the adequacy of their experience. The estimate for the N.S.W. Region in 1985 was 729 anaesthetics per trainee, so that approximately 70000 anaesthetics annually are given by these persons.

Not even as close an approximation as this is possible for specialists and non-specialists, although Health Insurance Commission statistics suggest that the proportion of anaesthetics given by specialists is in the vicinity of 85% of the total reimbursements under Medicare. Perhaps then the figure for specialists is approximately 400000

TABLE IX. *Status of anaesthetists involved in "anaesthetic deaths". †Includes dentists*

	1960–69	1970–80	1983–85	Whole series
Specialists	89 (27%)	111 (46%)	31 (62%)	231 (37%)
Non-specialists	186 (55%)	85 (36%)	8 (16%)	279 (44%)
Registrars	48 (14%)	37 (15%)	8 (16%)	93 (15%)
Residents	12 (3.5%)	4 (1.7%)	1 (2%)	17 (3%)
Other†	—	2 (0.8%)	2 (4%)	4 (0.6%)
Totals	335	239	50	624

administrations per year, and for non-specialists in the order of 70000, much the same as trainees. It is impossible even to guess at numbers for the remaining groups (residents, "others"), and it should be appreciated that even those numbers given above are estimates.

What is evident over the years of the survey is the declining gross contribution of the non-specialist. This certainly does reflect a continuing reduction in general practitioner involvement in anaesthesia—a process common to all developed countries, as specialization takes hold.

Although the registrar contribution remains constant as a proportion of deaths, absolute numbers in this category have declined, and the trainees themselves have increased in number from a mere 15 in 1960 to six times as many in 1985. Per anaesthetist, therefore, their performance is improving all the time, and this may be in part the result of better supervision.

The resident medical officer (R.M.O.) now makes little contribution, although the earliest results from the study revealed his or her role in mortality amongst "good risk" patients. This led to a phasing out of the R.M.O. as a service member of the anaesthetic work force.

TABLE X. *Classification of surgery as elective or emergency*

Urgency	1960–69	1970–80	1983–85	Total
Elective	135 (40%)	104 (44%)	25 (50%)	264
Emergency	200 (60%)	135 (56%)	25 (50%)	360
Total	335	239	50	624

Patients

There is a preponderance of emergencies throughout the series, which is neither surprising nor unusual in surveys of this type (table X). Hence it is one-and-a-half times more likely that a patient admitted as an emergency case will suffer anaesthesia-attributable death, but since emergencies make up less than 15% of the total surgical case-load, each individual undergoing emergency anaesthesia is at 10 times greater risk.

The risk status of patients for anaesthesia is classified by the Committee on the basis of the anaesthetist's own assessment. The American Society of Anaesthesiologists' five-category system is not used, because fewer than 50% of N.S.W. anaesthetists are familiar enough with the definitions to use the system accurately. The descriptive terms good, fair, poor and desperate are therefore used, and their lack of precision is acknowledged. It is fair to assume nevertheless, that a "good" risk patient is one in whom anaesthesia should not have been a problem,

TABLE XI. *Preoperative condition of patient and grade of anaesthetist involved in anaesthetic mortality*

	Condition of patient				
Anaesthetist	Good	Fair	Poor	Desperate	Totals
Years 1960–69					
Specialists	8	20	40	21	89
Non-specialists	45	47	88	6	186
Registrars	6	9	25	8	48
Residents	6	4	2	0	12
Total	65	80	155	35	335
Years 1970–80					
Specialists	19	37	38	17	111
Non-specialists	18	21	26	20	85
Registrars	2	12	16	7	37
Residents	1	2	—	1	4
Other	2	—	—	—	2
Totals	42	72	80	45	239
Years 1983–85					
Specialists	7	9	12	3	31
Non-specialists	1	1	5	2	9
Registrars	—	3	3	2	8
Residents	—	1	—	—	1
Others	1 (Dentist)	—	—	—	1
Totals	9	14	20	7	50

TABLE XII. *Ten commonest operations, 1960–69*

	Operation	No.
(1)	Laparotomy for obstruction	40
(2)	Laparotomy for peritonitis	29
(3)	Caesarean section	14
(4)	Appendicectomy	14
(5)	Laparotomy for gastrointestinal bleeding	12
(6)	Strangulated hernia	11
(7)	Cholecystectomy	10
(8)	Amputations	9
(= 9)	Forceps delivery	8
	Hysterectomy	8
	Tonsillectomy, adenoidectomy and post-tonsillectomy bleeding	8

TABLE XIII. *Ten commonest operations, 1970–80*

	Operation	No.
(1)	Laparotomy for obstruction	19
(2)	Laparotomy for peritonitis	18
(3)	Operations for fractured neck of femur	14
(4)	Caesarean section	9
(= 5)	Amputations	9
	Cholecystectomy	7
(= 7)	Abdomino–perineal resection	7
	Hysterectomy	7
(9)	Laparotomy for trauma	6
(10)	Total hip replacement	6

TABLE XIV. *Four commonest operations, 1983–85*

	Operation	No.
(1)	Internal fixation of fractured neck of femur	7
(2)	Laparotomy for obstruction	6
(3)	Austin Moore arthroplasty	5
(4)	Cataract extraction	3

whilst a desperate risk is one in whom severe life-threatening pathology was present. The results are shown in table XI which also includes the status of the anaesthetists involved.

Operations

Since emergencies predominate in the series, the common emergency operations also head the list of procedures. However, there have been interesting changes since the survey began. Tables XII and XIII show the 10 commonest procedures in 1960–69 and 1970–80, respectively, whilst table XIV lists the four commonest procedures in the much smaller group of deaths classified during 1983–85.

Although laparotomy for obstruction or peritonitis are predominant, interesting changes are evident in the lower ranking procedures. Noteworthy are reductions in obstetric catastrophes, and the disappearance of tonsil surgery from the "top 10". The entry of abdomino–perineal resection and hip surgery should be noted, especially the latter, which also seems to be associated with an increased usage of regional anaesthesia.

Incidence

Changes in the incidence of death in relation to anaesthesia in N.S.W. over 25 years are, to say the least, encouraging. Despite a population increase from 3.8 million to 5.5 million, and a higher incidence of surgery in that population, anaesthesia-attributable deaths are lower in both absolute and relative terms (table XV).

Estimates of the number of procedures carried out during the first 10 years of the survey are not as reliable as those later, but have been deliberately overestimated to place later ratios in the least favourable light. Thus it is likely that the true incidence of anaesthesia-attributable mortality was higher in the earlier years of the study than the table would indicate. However, recent figures are much more accurate and give as true a picture of the recent situation as is possible.

Taking all of these reservations into account, it would appear to be at least five times safer to undergo anaesthesia in 1987 as it was in 1960. This is even more so for a young and otherwise healthy person.

TABLE XV. *Incidence of deaths in relation to anaesthesia*

Year	No. of deaths	Population	Deaths per 100000	No. of anaesthetics (estimated)	No. of administrations per death
1960	55	3.8×10^6	1.45	300000	1 in 5500
1970	39	4.5×10^6	0.87	400000	1 in 10250
1984	24	5.5×10^6	0.44	550000	1 in 26000

TABLE XVI. *Fellows of the Faculty of Anaesthetists, R.A.C.S.*

Year	No. of Fellows in Australia	No. of Fellows in N.S.W.
1960	106	39
1970	306	122
1984	1115	416

CONCLUSIONS

A 25-year survey of anaesthesia-attributable mortality covers most of the clinical life-time of a specialist anaesthetist. Those who were in practice in 1960, and remained clinically active 25 years later would have been aware of many changes. One of the most spectacular has been the increase in numbers of trained anaesthetists serving the population (table XVI).

Concomitant with this increase has been an increase in the influence of the Faculty of Anaesthetists, and a recognition by hospitals and health authorities of its credentials as a standard-setting body, not only for the training environment necessary for candidates sitting its Diploma of Fellowship, but also for the clinical practice of anaesthesia.

Surgeons and obstetricians expect better anaesthesia, and complain when they do not get it, and even patients are more aware of the significance and importance of the anaesthetic (and the anaesthetist) than they once were. The impact of anaesthesia mortality committees is more difficult to estimate. The N.S.W. Special Committee was the first in Australia, and has been followed by Committees in South Australia, Queensland, Victoria and Western Australia. Three of these have published reports and drawn attention to certain areas of clinical significance (Anaesthetics Mortality Committee, 1975, 1985; Committee, 1978; Consultative Council, 1983, 1985). There is now an effective Committee in New Zealand.

Anaesthetists in New South Wales respect their Committee, co-operate with it, and are proud of its primogeniture. This attitude to what is, after all, a voluntary peer review exercise is probably sufficient evidence that the Committee is a factor in the continuing improvement in anaesthesia-attributable mortality. What is certainly important is that an accurate quantitative index of that mortality is available, enabling attention to be focused on any deterioration. It is an axiom of problem solving that solutions are difficult without data on the magnitude or nature of the problem. Anaesthesia mortality studies, given adequate notification facilities, a guarantee of confidentiality and continuity of operation, can provide valuable information on standards of health care and contribute to an improvement in those standards.

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ANAESTHETIC CONTRIBUTION TO MATERNAL MORTALITY

M. MORGAN

The Confidential Enquiries into Maternal Deaths in England and Wales are unique in British medicine in that they appraise systematically the results of medical work. The original enquiry was started in 1928, but was completely revised in 1952, since when there have been 10 reports covering a period of 30 years. Each maternal death is reviewed carefully to ascertain if additional or different action might have given the mother a better prospect of survival.

The difficulties in collecting accurate information retrospectively in this type of report are well known, as is their examination from an elitist standpoint. It is a feature, however, that each successive one is more complete than its predecessor, because of the free participation of all those who have been concerned with the mother's care and who realize the importance of the enquiries. This is particularly true for anaesthesia, practitioners of which are much concerned with anaesthetic mortality and wish to pinpoint those areas where improvements can be made. Another unique feature is the "retrieval rate", which is almost 100%. Thus the causes of virtually all anaesthetic deaths from 1952 to 1981 are known.

The purpose of this paper is to examine the causes of anaesthetic related maternal mortality as presented in these enquiries.

CONFIDENTIAL ENQUIRIES INTO MATERNAL DEATHS

Maternal death

It is agreed internationally that maternal deaths are either direct or indirect. The International Classification of Disease, Ninth Review (ICD 9) (Classification, 1977) defined *direct* obstetric deaths as "those resulting from obstetric complications of the pregnant state (pregnancy, labour and the puerperium), from interventions, omissions, incorrect treatment, or from a chain of events resulting from any of the above." Thus in this context, anaesthesia is regarded as an intervention. *Indirect* deaths are "those resulting from previous existing disease, or disease that developed during pregnancy and which was not due to direct obstetric causes, but which was aggravated by physiologic effects of pregnancy."

ICD 9 defines a maternal death as "the death of a woman while pregnant or with 42 days of termination of pregnancy, irrespective of the duration and site of the pregnancy, from any cause related to or aggravated by the pregnancy or its management but not from accidental or incidental causes." Walker (1986) has pointed out that such a time interval is likely to exclude a substantial and increasing proportion of maternal deaths, since increasing expertise in resuscitation and intensive care allows patients to be kept alive for much longer periods. Support for his views comes from the observations of Rochat and colleagues (1981) who, in a study in Georgia, found that the 42-day limit excluded 17% of deaths from maternal causes. They suggested that increasing the interval to 90 days would increase the detection of maternal deaths without including an excessive number of non-maternal deaths.

The most recently published enquiry (Report, 1986), however, has included deaths that have occurred between 43 days and 1 year after delivery and abortion. These are now termed "late" deaths and are dealt with in a separate chapter in the report, but include none related to anaesthesia.

Mechanism of the enquiry

The basic mechanism of the enquiry is shown in figure 1. The instigator of an investigation of a maternal death is the District Medical Officer (DMO) of the area in which the mother was

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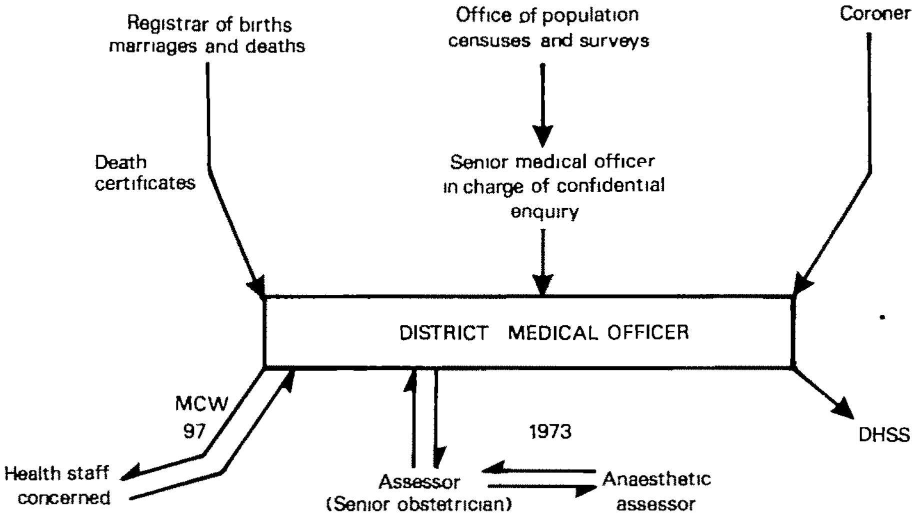
Registrar of births marriages and deaths
Office of population censuses and surveys
Coroner
Death certificates
Senior medical officer in charge of confidential enquiry
DISTRICT MEDICAL OFFICER
MCW 97
Health staff concerned
1973
Assessor (Senior obstetrician)
Anaesthetic assessor
DHSS

FIG. 1. Mechanism of confidential enquiries into maternal deaths in England and Wales. The basis for collection of information is form MCW 97, which is completed by all health staff who have been concerned with the care of the mother. Since 1973, the obstetric assessor (one in each region in England and Wales) obtains the opinion of the anaesthetic assessor for that region if an anaesthetic, local or general, has been given. (Reproduced by kind permission of the Royal Society of Medicine.)

usually resident, who receives copies of all death certificates. There is no requirement for anyone involved in a mother's care to report a death. An enquiry form (MCW 97) is sent to general practitioners, health visitors, community physicians, consultant obstetricians and any other relevant staff who have been concerned with her care. This form has recently been altered so as to encourage reporting not only of failures of clinical care, but also of any other factors leading to a low standard of care, such as shortage of resources for staffing, administrative failures and inadequate back-up facilities.

The completed form is returned to the DMO, who then sends it to the regional obstetric assessor. Since 1973, a regional anaesthetic assessor has reviewed all cases who have received an anaesthetic, and there is no doubt that this has resulted in a marked improvement in the report, from an anaesthetic point of view. Terms such as "hypoxic cardiac arrest" have now disappeared and the classification of anaesthetic-related mortality is more meaningful. The form MCW 97 is sent subsequently to the Chief Medical Officer at the Department of Health and Social Security, where the Department's central assessors in obstetrics and gynaecology, anaesthetics and histopathology prepare the final report from all the available information. At all stages, strict confidentiality is maintained. The names of the mothers are erased from all forms, and the latter are destroyed after publication of the report. The delay in the appearance of the latest report resulted from problems with confidentiality, resulting in temporary suspension of the enquiry for 8 months, in addition to industrial action and to transfer of the responsibility for initiation of the report to the DMO (Cloake, 1986).

The actual number of deaths in each triennium since 1952 is shown in table I. One of the most disturbing aspects is the number of deaths associated with avoidable factors, where there has been a departure from accepted anaesthetic practice. This particular term has been omitted from the latest report as it implied that, if a particular course of action had been avoided, the patient would not have died. It has been replaced by the term substandard care, which also encompasses administrative failure as already mentioned. It would be correct to comment that much higher standards are now expected of anaesthetists than would have been at the inception of these reports.

In most instances, the primary factor leading to the mother's death is obvious and can easily be classified. Many deaths have more than one cause,

TABLE I. *Maternal mortality figures obtained from the* Confidential Enquiries into Maternal Deaths In England and Wales. **This term has been replaced by "substandard care", first used in 1979–81*

Years	Maternal mortality per 1000 total births	Number of deaths from anaesthesia	Percentage true maternal deaths from anaesthesia	Percentage with avoidable factors*
1952–54	0.53	49	4.5	—
1955–57	0.43	31	3.6	77
1958–60	0.33	30	4.0	80
1961–63	0.26	28	4.0	50
1964–66	0.20	50	8.7	48
1967–69	0.16	50	10.9	68
1970–72	0.13	37	10.4	76
1973–75	0.11	31	13.2	90
1976–78	0.11	30	13.2	93
1979–81	0.11	22	12.2	100

and here the assessor attempts to select the factor most likely to have caused death. As a result, therefore, the major causes of anaesthetic-related mortality have been identified and have indicated the direction of required research and teaching.

MAJOR CAUSES OF DEATH

The majority of anaesthetic deaths are associated with induction of general anaesthesia and result from two main causes, namely inhalation of gastric contents and failure to intubate the trachea (which in turn may provoke the former).

Inhalation of gastric contents

The problem of gastric acidity

The first description of the inhalation of gastric contents in obstetric patients was by Hall (1940), who coined the term chemical pneumonitis. The problem was highlighted by Mendelson (1946), who described an asthma-like syndrome resulting from inhalation of liquid gastric contents. Mendelson performed animal experiments which showed the severe reaction that resulted from instillation of unneutralized gastric juice or hydrochloric acid 0.1 mol litre^{-1} to the lungs, all the animals dying within a few hours. Further work by Teabeaut (1952) in rabbits showed that the severity of the pulmonary lesions was related to the pH of the gastric aspirate, the critical value being 2.5. This is the value accepted by most anaesthetists as being that below which severe pulmonary damage occurs (Vandam, 1965). Supporting evidence for this value comes from a small series of non-obstetric patients reported by Lewis, Burgess and Hampson (1971). They related mortality following aspiration to the pH of the aspirate: 100% when the pH was < 1.75, 25 % when the pH ranged from 1.75 to 2.4, but no deaths when pH was greater than 2.4.

Because of the severity of acid aspiration, it was logical that attempts should be made to increase the intragastric pH above the so-called critical value, and the methods of achieving this have recently been reviewed (Morgan, 1984). The main methods involve either regular antacid therapy or inhibition of gastric acid production with H_2-receptor antagonists. Mist.magnesium trisilicate B.P., although effective in increasing intragastric pH, has the disadvantages that it does not mix well with gastric contents and should be recently prepared (Crawford and Potter, 1984). It is also particulate, and antacids of this type have been shown themselves to cause a severe reaction when instilled to the lungs (Gibbs et al., 1979). Sodium citrate is unpalatable, has a short shelf-life and would appear not to be as reliable as mist.magnesium trisilicate in increasing intragastric pH (White, Clarke and Stanley-Jones, 1976; Hester and Heath, 1977; Dewan et al., 1982). Despite its drawbacks, mist.magnesium trisilicate remains the most widely used antacid in the U.K. (Sweeney and Wright, 1986).

The main drawback of the H_2-receptor antagonists is that they do not have any effect on acid that has already been produced and remains in the stomach. Timing of administration is therefore critical, although they can be combined effectively with a single dose of antacid (Gillett, Watson and Langford, 1984). Cimetidine is associated with a number of side effects, and in particular inhibits drug metabolizing enzymes in the liver involving anticoagulants, barbiturates, benzodiazepines, propranolol and theophylline (Manchikanti, Kraus and Edds, 1982). It may result in significant hypotension when given by the i.v. route (Hammond and Ware, 1983). Ranitidine has far fewer side effects, is longer acting, but is also slower in onset than cimetidine.

As it is not known which mother might require an anaesthetic in labour, it is the routine in the majority of units in the U.K. for all mothers to receive some form of therapy to increase intragastric pH. This practice has been questioned recently by Thorburn and Moir (1987), who calculated that, if antacid therapy was practised routinely for all mothers in labour in England and Wales, some 800000 mothers per year would receive it in the hope of preventing the death of four, and that approximately 700000 mothers would have received therapy for a disorder from which they had not been at risk in the first place. They studied 100 patients undergoing emergency Caesarean section, giving cimetidine 200 mg i.m. when the decision to perform the operation was made, and 30 ml of sodium citrate 0.3 mol litre^{-1} by mouth preceding general anaesthesia. These patients had not received routine antacid therapy during labour. No patient had a gastric aspirate of pH less than 2.7 and only one less than 3.0. These figures are certainly no worse than those obtained from studies on routine antacid therapy.

The assumption made in the maternal mortality reports that those who have inhaled gastric contents died from acid aspiration is not valid, as in no instance was the pH of the aspirated material reported. Indeed, it would be reasonable to assume that the pH would have been greater than the critical value in most of these mothers. Taylor and Prys-Davies (1966) found that 57% of mothers who had not received antacid therapy had an intragastric pH greater than 2.5, and since that time such therapy has become routine in British obstetric practice.

Is there, therefore, a continued need for antacid therapy? There are several reports of severe lung damage and death following aspiration of gastric contents containing antacids (Bond, Stoelting and Gupta, 1979; Heaney and Jones, 1979; Whittington, Robinson and Thompson, 1979). The increasing use of antacids in labour has not been associated with a reduction in mortality from inhalation (Reynolds, 1983). On the other hand, Crawford and Opit (1976) found a striking relationship between provision of antacid prophylaxis and the sequelae of aspiration, while Hutchinson (1979) reported that the frequency of severe acid aspiration decreased from 1:11000 to 1:40000 when magnesium trisilicate came into routine use.

Animal work (James et al., 1984) has shown that even a small volume of fluid instilled to the lungs is associated with a high mortality if the pH is low. If gastric fluid was buffered effectively, much higher volumes than previously thought, could be tolerated. Little work has in fact been undertaken on the relationship between pH and the volume that has to be inhaled to produce lethal results. In adults, the critical volume of fluid of pH less than 2.5 is accepted as 25 ml, but this value is that quoted by one group of workers who refer to preliminary unpublished work (Robert and Shirley, 1974).

It may, therefore, be concluded that efforts should continue, to increase the intragastric pH in obstetric patients, but the most effective and reliable method and most appropriate agents of doing this have yet to be found. It is important, however, that anaesthetists do not become complacent and believe that inhalation of gastric contents of high pH is a benign process, and therefore abandon methods of preventing regurgitated material from entering the lungs. The consequences of inhalation depend not only on the pH of the aspirate, but also on the amount and distribution within the lungs and the presence or absence of food, particulate matter and bacteria (Wynne and Modell, 1977). Schwartz and colleagues (1980) have shown that gastric contents at pH 5.9 can produce pulmonary changes that are as severe as those produced by hydrochloric acid at pH 1.8.

Intragastric volume

The factors affecting gastric emptying have been reviewed by Nimmo (1984), and it should be the aim of every anaesthetist to keep the stomach empty (Reynolds, 1983). In modern obstetric practice, prolonged labour is avoided and hence there is no longer any need to give fluids by mouth, as fluid requirements may be administered i.v.

Among the most potent factors delaying gastric emptying are opioid analgesics (Nimmo, Wilson and Prescott, 1975; Todd and Nimmo, 1983). The majority of instances of inhalation of gastric contents occur during induction of general anaesthesia for Caesarean section and it is mentioned frequently in the Confidential Enquiries that labour was prolonged. It is these mothers who could well have received large doses of opioids. Repeated doses of opioids should be avoided in labouring women and other forms of analgesia should be made available. In the absence of mechanical obstruction, opioid analgesics are the major cause of delayed gastric emptying in the perioperative period, while regional analgesic techniques are without important effects (Nimmo, 1984). Holdsworth (1978) found the mean intragastric volume in labour to be 22 ml in those who had extradural analgesia, compared with 50 ml in those without.

It is no longer routine to empty the stomach before induction of general anaesthesia in obstetric patients. The exceptions would be those who have taken a recent meal or been in labour for many hours and have received several doses of an opioid analgesic. The various methods of emptying the stomach have been discussed by Morgan (1984).

Prevention of inhalation of regurgitated material

I.v. induction of anaesthesia is almost universal in obstetrics, so that active vomiting is not a problem. In *all* obstetric patients, induction must be accompanied by efforts to prevent any regurgitated material from entering the lungs. The danger period is the time from loss of consciousness until the airway is secured by a cuffed tracheal tube.

Lower oesophageal sphincter (LOS) pressure. One approach to the prevention of regurgitation is to increase the tone of the LOS. Metoclopramide has been shown to increase the sphincter pressure (Brock-Utne et al., 1976; Laitinen et al., 1978) and, apart from this drug and domperidone, most other drugs have a depressant effect on LOS tone, thereby facilitating any propensity to regurgitation (Cotton and Smith, 1984). However, atropine, which is frequently given i.v. at induction, consistently decreases LOS tone, but the effect is not evident until 3 min after administration (Cotton and Smith, 1981), when tracheal intubation would already have been performed. Furthermore, Skinner and Camp (1968) showed that, although atropine decreased the sphincter pressure, it did not increase the incidence of reflux, suggesting that pressure is not the only factor associated with reflux. This is in direct contrast to the findings of Fisher and colleagues (1977).

Conflicting results have also been reported of a combination of atropine and metoclopramide on LOS tone. Thus Brock-Utne and colleagues (1976) showed that a combination of metoclopramide 10 mg and atropine 0.6 mg i.v. given simultaneously produced no change in barrier pressure. However, Cotton and Smith (1981) showed that the effect of atropine predominated when the two drugs were given consecutively, irrespective of the order of administration.

It is very difficult to envisage that administration of a drug will result in such an increase in LOS pressure that it will prevent regurgitation at induction of anaesthesia. Reliance should not be placed on this method of preventing aspiration of gastric contents.

Position at induction. Goodrich (1979) has recommended that all anaesthetists should be proficient at induction of anaesthesia and tracheal intubation in the head-down, left-lateral position. This ensures that any regurgitated material cannot enter the lungs but, although acceptable as a general principle, it is not really a practical proposition in obstetrics because of the difficulties of turning and keeping a mother at term, attached to monitoring equipment, in this position. Induction in the lithotomy position should be avoided whenever possible, because the associated increase in intragastric pressure makes regurgitation more likely, but there are a few rare occasions, for example after-coming head of a breech, when it is necessary. Tracheal intubation under local analgesia is not a feasible technique for the majority of obstetric patients.

Cricoid pressure. Rosen (1981) pointed out that approaches to the subject of prevention of aspiration abound, but that the lynchpin of physical prevention is correct application of cricoid pressure. Despite the fact that it has been used in many hundreds of thousands of obstetric cases, in the literature there is only one record of failure of cricoid pressure (Whittington, Robinson and Thompson, 1979). There are, however, many reports of deaths after either failure to apply cricoid pressure or its release before passage of a cuffed tracheal tube. Enquiries of examination candidates, and observations of junior anaesthetic staff, nurses and operating department assistants indicate that the majority do not apply cricoid pressure in the recommended manner. The fault for this must lie with consultant staff for not teaching, and ensuring, the correct application of the technique.

The method of application of cricoid pressure as described by Sellick (1961) is shown in figures

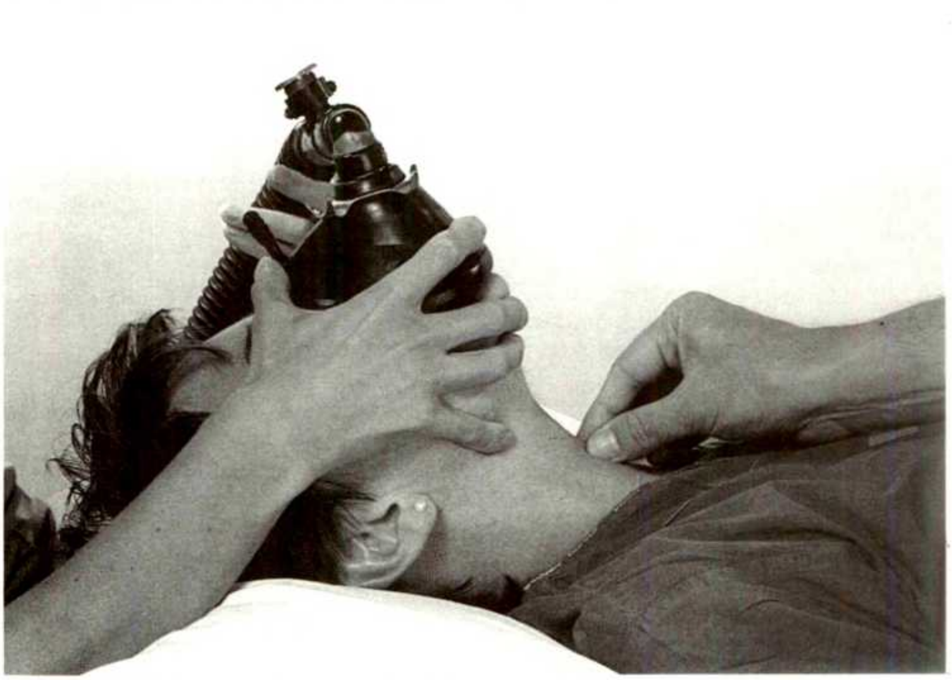

FIG. 2. Application of cricoid pressure. The patient's head rests on a pillow and the neck is extended so that the cervical vertebrae and hence the oesophagus are brought forward, thereby making it easier to occlude.

2 and 3. "*Before induction the cricoid is palpated and lightly held between the thumb and second finger; as anaesthesia begins, pressure is exerted on the cricoid cartilage mainly by the index finger.*" He also stressed that the neck should be extended, bringing the cervical vertebrae forward so that it is easier to occlude the oesophagus by backward pressure on the cricoid. He showed radiologically that contrast media maintained at a pressure up to 94 cm H_2O could be prevented from passing beyond the point of application. Sellick showed not only that this method effectively prevented regurgitated material from entering the pharynx, but also that "*During cricoid pressure the lungs may be ventilated by intermittent positive pressure without the risk of gastric distension.*"

Cricoid pressure must be applied before loss of consciousness and, although not comfortable, is well tolerated by the majority of patients. Recent work has shown that a force of 44 N is required to protect the majority of adults from regurgitation (Wraight, Chamney and Howells, 1983). The same group also showed that there was an unacceptably wide variation in performance of anaesthetists and paramedical personnel familiar with the manoeuvre, and that 47% failed to reach a force of 44 N (Howells et al., 1983). The importance of correct application of the simple and effective procedure of cricoid pressure and its maintenance until the trachea has been sealed by a cuffed tube cannot be overstressed.

Because fatalities do still occur as a result of incorrect application of cricoid pressure, Lawes and colleagues (1986) have designed an instrument to provide consistent and reproducible cricoid pressure at a force of 44 N. In the initial studies it was shown that the skill required to use the instrument was easily learned, but that it did increase the incidence of poor intubating conditions, mainly from distortion of the larynx. It is difficult to see how an instrument such as this is going to replace the simple manoeuvre of manually applied cricoid pressure.

Failed Tracheal Intubation

When the Confidential Enquiries commenced, tracheal intubation was rarely performed during obstetric anaesthesia. It was after the work of Hodges and colleagues (1959) that routine intubation after thiopentone and suxamethonium

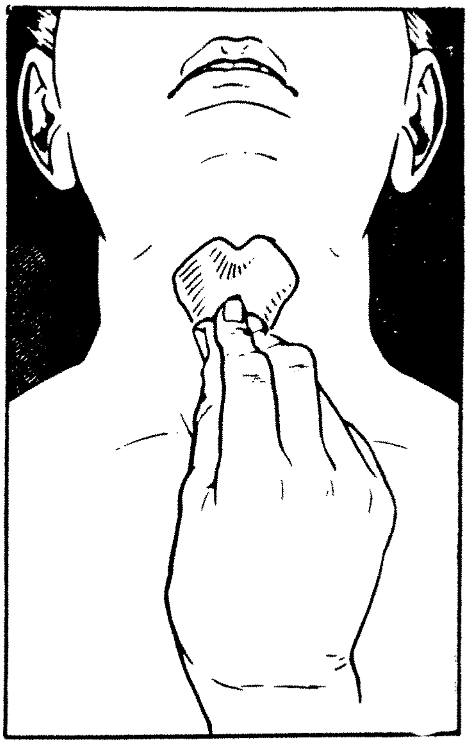

FIG. 3. Diagram of the correct application of cricoid pressure. The cricoid is held between the thumb and second finger and backward pressure is exerted on the cricoid cartilage mainly by the index finger. (Reproduced by kind permission of Dr B. A. Sellick and the Editor of the *Lancet*.)

became accepted practice. It was in the report for the years 1964–1966 (Report, 1969) that technical difficulties with tracheal intubation were first mentioned and it is noteworthy that, in those years, the percentage of true maternal deaths from anaesthesia more than doubled. This is probably the time at which the thiopentone–suxamethonium induction sequence came into widespread use. Inability to intubate the trachea in an apnoeic patient is a life-threatening situation that demands immediate skilled action. Since that time, difficulty with tracheal intubation has been increasingly implicated as a factor contributory to maternal deaths.

There is little doubt that it is more difficult to intubate the trachea in obstetric patients than in their non-obstetric counterparts. For the years 1979–1981 (Report, 1986), eight of 22 deaths were directly related to difficulties with tracheal intubation, whereas the report of Lunn and Mushin (1982) cited only four problems with tracheal intubation of 58 anaesthetic deaths in non-pregnant patients. There are a number of reasons for this. The mothers usually have full dentition and the thorax has been lifted into an unusual position by a wedge. Some degree of laryngeal oedema may be present, particularly in the presence of pre-eclamptic toxaemia (Brock-Utne, Downing and Seedat, 1977; Mackenzie, 1978). Incorrect application of cricoid pressure may distort and displace the larynx, while the presence of large breasts and a hand applying cricoid pressure may make introduction of a laryngoscope difficult. As a result, cricoid pressure may be released, with possible regurgitation and aspiration.

In the haste to pass a tracheal tube, attempts at laryngoscopy may be made too soon, before the suxamethonium has taken its full effect, and might have the effect of precipitating vomiting or regurgitation. Carmie, Street and Kumar (1986) found that junior anaesthetists attempted laryngoscopy much earlier in relation to the observed degree of neuromuscular blockade in obstetric patients (mean time 29.8 s) than in ordinary surgical patients (mean time 63.5 s). They proposed that the junior anaesthetists, who were unaware of the degree of blockade, were either reluctant to wait or found it difficult to judge complete blockade clinically. Objectively, it has been shown by Donlon, Ali and Savarese (1974) that, although conditions were not perfect, tracheal intubation could be achieved easily by relatively inexperienced anaesthetists once the twitch height of the adductor pollicis has been depressed by 95% of its control value. Blackburn and Morgan (1978) found that the mean time to this point in lightly anaesthetized patients following suxamethonium 1.0 mg kg^{-1} was 49.2 s (SEM 1.68). It is imperative that sufficient time be given for the suxamethonium to exert its full effect. To achieve rapid paralysis, a minimum of suxamethonium 100 mg should be given, preceded by atropine. Anaesthetists should be reminded that administration of a small dose of a competitive neuromuscular blocking drug before the depolarizing drug, in the hope of preventing the increase in intragastric pressure or reducing the incidence of muscle pains after operation, will antagonize the effect of the suxamethonium and make intubation more difficult.

The incidence of failed intubation in obstetric anaesthesia is not known, but Lyons (1985) quotes a figure of 1:300 over a 6-year period. This high incidence is almost certainly because a failed intubation drill is advocated early in the course of a difficult intubation in that unit (Lyons and MacDonald, 1985). However, Samsoon and Young (1987) have also reported a similar incidence of failure to intubate the trachea of obstetric patients, namely 1 in 280 over a 4-year period, compared with 1 in 2230 in surgical patients.

Cormack and Lehane (1984) have classified difficulty of intubation into four grades according to the view obtained at laryngoscopy. They suggested that the main cause of trouble was grade 3, in which the epiglottis can be seen, but not the cords. Such cases are quite rare, but they calculated that each anaesthetist would encounter this problem about four times before becoming a consultant, while about 2% can expect to become consultants without having met the situation. They suggest a method whereby the problem can be simulated in routine anaesthesia so that a drill for managing it can be practised. This is recommended to all anaesthetists.

It is not always possible to predict from usual clinical observations whether tracheal intubation will be difficult. Mallampati and colleagues (1985) have suggested a relatively simple sign to predict difficulty in tracheal intubation, which involves the ability to visualize the pillars of the fauces, soft palate and base of the uvula when the patient opens the mouth and protrudes the tongue maximally whilst in the sitting position. They found that the degree of difficulty in visualizing these three structures was an accurate predictor of the ease of direct laryngoscopy.

As difficult intubation is therefore a relatively common occurrence in obstetrics, it is imperative that equipment necessary to deal with the problem is always immediately at hand. Skilled assistance is also necessary. Not only must laryngoscope blades of different sizes be available, but also those where the angle between the blade and the handle allow for easier introduction to the mouth in appropriate circumstances — for example the polio blade and that described by Jellicoe and Harris (1984). A new angled laryngoscope has recently been described by Bellhouse, which can accommodate a prism if it is required for difficult intubations (Tunstall and Sheikh, 1986). As yet, there are no reports of experience with this instrument in the U.K.

Everyone who practises obstetric anaesthesia is going to meet a patient whose trachea cannot be intubated. Thus it is essential that, under these circumstances, a failed intubation drill is instituted which is understood by all labour ward staff. There can be no hard and fast rule as to what form this should take, as it depends on individual circumstances, but that suggested by Tunstall (1976) and Tunstall and Sheikh (1986) would form a sound basis. The most important factor in this situation with an apnoeic patient is a prompt decision that a tracheal tube cannot be passed and that the lungs must be ventilated. Scott (1986) has stressed that patients do not die from failure to intubate, they die from failure to stop trying to intubate. The mother at term is utilizing oxygen at a greater rate than when not pregnant (Archer and Marx, 1974), and this will be compounded if cardiac output is reduced by an element of inferior vena cava occlusion. All anaesthetists must be capable of ventilating the lungs using a mask, airway and bag; correctly applied cricoid pressure will prevent inflation of the stomach during the procedure. The failed intubation drill should be practised and it is true to say that the first time this is used should not be the first time when it is essential.

If ventilation with a face mask is difficult, then deliberate passage of a tracheal tube or some form of specially designed tube into the oesophagus may allow the lungs to be ventilated until spontaneous breathing returns. Both have been described, with successful outcomes, following failed intubation in obstetrics (Boys, 1983; Tunstall and Geddes, 1984). Anaesthesia with spontaneous ventilation should continue using a volatile agent with which the anaesthetist is familiar and in a concentration which allows safe completion of surgery.

Oesophageal intubation. The other cause of death following difficult tracheal intubation is undiagnosed oesophageal intubation. The signs of the latter should be obvious, but this is not always so and experienced anaesthetists can be misled into believing that an incorrectly placed tube is in the trachea, even after the appearance of cyanosis (Howells and Reithmuller, 1980). They recommended that ventilation should be carried out with a mask over the open tube, when relief of cyanosis would indicate misplacement of the tube. Presence of carbon dioxide in the exhaled gas, however, is the only absolute diagnostic test of correct placement of a tracheal tube.

A high level of suspicion of oesophageal intubation should be borne in mind, remembering that pre-oxygenation will delay the onset of cyanosis, possibly until after delivery of the baby. Gray (1985) has surveyed serious anaesthetic accidents and concluded with six very simple maxims, the first of which is "when in doubt, take it out."

OTHER CAUSES OF DEATHS

By far the largest number of deaths occur during, or as a result of mishaps occurring at, the induction of general anaesthesia. Of the other deaths, attempts have been made to classify them into distinct groups.

Misuse of drugs

The two main groups of drugs involved are central sedatives and neuromuscular blockers. The effects of the former on ventilation, particularly when used in combination, are repeatedly stressed in the reports. Use of opioids with i.v. anaesthetics such as methohexitone, and often with a benzodiazepine, would appear to be relatively common for minor procedures such as termination of pregnancy. The situation is compounded by the use of opioid premedication. Benzodiazepines have little effect on ventilation in healthy adults, but potentiate the central effects of other sedatives. Such drug combinations are potent central depressants and the development of any element of ventilatory obstruction in a heavily sedated patient whose ventilation is already depressed can have disastrous consequences.

Inadequate antagonism of neuromuscular blockade is another aspect mentioned in the reports. Caesarean section is a relatively rapid procedure and antagonism of blocking drugs may be required quite soon after their administration, particularly as tracheal intubation has been achieved with the aid of suxamethonium. With the availability of shorter acting agents such as atracurium, the use of pancuronium and tubocurarine for Caesarean section must now be questioned. Initially, reversal of these drugs might appear clinically to be adequate, but this can be difficult to judge in a patient who is drowsy from the effects of an anaesthetic, which has probably included an opioid with its accompanying ventilatory depressant effects. With the considerable amount of stimulation that occurs at the end of surgery, the patient's tidal volume and colour might well appear adequate. However, on moving to the quieter environment of a possibly inadequately staffed recovery room or a general ward, the patient might lapse back into sleep. If there is any residual weakness from the effects of the blocking drug, muscle power could be inadequate to overcome any ventilatory obstruction, and death ensue. The only objective signs of adequate neuromuscular transmission are provided by a nerve stimulator, use of the train-of-four stimuli indicating adequate motor power even in the absence of a control response.

Frequent mention is made of the difficulty in identifying cyanosis in dark-skinned patients, whose deaths are often quoted as being associated with the above drugs. Great care must be taken when any ventilatory depressant drug is used in these patients. It is also pertinent to remember that hypoxia is a cause of restlessness, and after operation this must be excluded before administration of an opioid.

Several drugs used in anaesthesia have a tendency to cause bradycardia, including suxamethonium, fentanyl and halothane. Recent reports have linked the use of vecuronium to the development of bradyarrhythmias and even asystole (Kirkwood and Duckworth, 1983; Milligan and Beers, 1985; Clayton, 1986; Pollock, 1986). This is most likely to occur in patients already at risk of bradycardia or during parasympathetic stimulation by peritoneal stretching. Routine use of atrophine i.v. is, therefore, advocated during induction of anaesthesia for Caesarean section.

Ergometrine has been implicated in causing inhalation of vomitus in a patient during Caesarean section under extradural analgesia. The drug should not be used in this way i.v. in conscious patients because of the high incidence of nausea and vomiting.

Any death from misuse of drugs is avoidable. Basic anaesthetic training requires a detailed knowledge of pharmacology, complications of drug therapy and drug interactions, but obstetricians must also be aware of all the actions of the drugs that they use and, in particular, of the dangers of sedative drugs and the drug combinations mentioned above. Operator–anaesthetists, alluded to more than once in the enquiries, can only be condemned. A much wider question, of course, is why the person involved did act as operator–anaesthetist.

Extradural analgesia

Since extradural analgesia became popular in 1968, use of the technique has been associated with eight deaths. On two occasions, the extradural was performed by an obstetrician.

Extradural analgesia is associated with potentially lethal complications, the signs of which must be recognized by all who practise the technique. Constant monitoring of a mother in receipt of an extradural is mandatory. All attendants must be familiar with the symptoms, signs and management of hypotension, and the importance of avoiding aortocaval compression cannot be overstressed. More difficult to recognize is the accidental intrathecal injection of local anaesthetic, particularly by those who do not regularly perform spinal anaesthesia. Similar remarks apply to the systemic toxic efforts of local anaesthetics. It is therefore obvious that someone who is versed in the management of all these complications, and of cardiac arrest, must be immediately available to attend the labour ward at all times.

In fact, serious complications of extradural analgesia are rare, Crawford (1985) detailing only nine potentially life-threatening events in 27000 extradurals provided for pain relief in labour. Corresponding figures are not available for Caesarean section under extradural analgesia. As most of the anaesthetic–related maternal mortality is associated with general anaesthesia for Caesarean section, it is not surprising that a change to extradural anaesthesia has been advocated. Davis (1982) suggested that the general anaesthetic rate for Caesarean section could be reduced to as little as 22% by making maximum use of extradurals. Corall (1982) however, queried if adoption of this policy would reduce maternal mortality, as the problems of induction of general anaesthesia would be replaced by the equally potentially serious, although different, ones of the extradural analgesia. There can be little doubt that increasing use has been made of regional anaesthesia for Caesarean section in the past 10 years, but it is too early yet to comment on whether or not this has resulted in a reduction in maternal mortality. It is heartening to know that in the last enquiry, covering the years 1979–1981, there were no deaths associated with extradural analgesia. Anaesthetists should not lose sight of the fact, however, that general anaesthesia will always be required for some Caesarean sections, and they must strive to maintain high standards.

It should also not be forgotten that, with the improvement in resuscitation services, some mothers who have had life-threatening complications have been resuscitated and have survived with extremely serious complications. Morbidity is outside the scope of the Confidential Enquiries.

Misuse of apparatus

Occasional deaths still occur from accidents with anaesthetic apparatus. Despite the fact that familiarity with apparatus and methods of checking its correct function are repeatedly stressed during training and represent frequent questions in examinations, it is evident that such advice is sometimes ignored. There is no need for sophisticated ventilators in a delivery suite, or for complicated alarm systems. All that is required is that the anaesthetist devotes all his attention to the mother and makes simple observations of her heart rate, arterial pressure and colour. Continuous display of the ECG should be a mandatory feature of all anaesthetics and the arguments for a capnograph on all labour wards are strong.

A responsible person should be designated to check all anaesthetic and related equipment daily and to ensure that spares are available for such items as tracheal tubes, laryngoscope bulks and batteries, etc. Regular servicing is essential.

ASSOCIATED FEATURES

The foregoing has concentrated on the causes of maternal death that can be gleaned from the triennial enquiries, but there are a number of other factors that have a bearing on anaesthetic-related maternal deaths.

Experience of the anaesthetist

The most important single factor associated with anaesthetic mortality is the experience of the anaesthetist in obstetric anaesthesia, which does not necessarily equate with status. In many instances the assessor is moved to comment that the skill and knowledge of the anaesthetist were inadequate for the task in hand. This is illustrated in the most recent report, in which it was obvious that the serious anaesthetic problems presented by patients with kyphoscoliosis were not familiar to the anaesthetist. Not only is an experienced anaesthetist more likely to anticipate potential problems, but s(he) would also be more likely to insist on appropriate equipment and help and correct resuscitation of the mother, where necessary, before starting the anaesthetic.

The importance of the experience of the anaesthetist is attested by reports from two large obstetric units. Morgan (1980) reported that anaesthesia was the commonest cause of death over a 20-year period, all the anaesthetics being given by junior staff with varying degrees of experience. This contrasts to the report of Breheny and McCarthy (1982) that, over a similar period, anaesthesia contributed to only two maternal deaths in high-risk mothers, the vast majority of the anaesthetics being given by consultants. It is the recommendation of the Obstetric Anaesthetists' Association that no one should give an anaesthetic unsupervised on the labour ward until they have had at least 1 year's experience.

There is also some indirect evidence to support the fact that obstetric anaesthetics should be given by experienced personnel. Maternal mortality in England and Wales in 1982 was 7 per 100000 live births, compared with 18 in Japan (Rosen and Fujimora, 1985). The prevalance of obstetricians and paediatricians is similar in the two countries, but that for anaesthetists is five times less in Japan. Although the maternal anaesthetic mortality rate is not known in Japan, it is known that 50% of anaesthetics for Caesarean sections in district general hospitals are given by obstetricians.

Haemorrhage

This is not an anaesthetic cause of death, but the anaesthetist is in the ideal position to cope with the problem. Any anaesthetist should be able to recognize the presence of hypovolaemia and be adept at central venous pressure monitoring and its interpretation. A drill is necessary for the management of severe haemorrhage, which should include the provision of additional staff to help with the emergency. Blood and blood substitutes must be readily available and help from a haematologist is required when disorders of coagulation are suspected and to resolve problems resulting from replacement of the circulating volume. Guidelines have been documented for the management of major obstetric haemorrhage (Report, 1986).

Administrative responsibility

Form MCW 97 has now been modified so as to obtain information regarding any administrative failures that have resulted in substandard care and, ultimately, maternal death. That anaesthetic services are giving cause for concern is highlighted by a recent survey in the Yorkshire region (MacDonald and Webster, 1986). This showed that a 24-h extradural service was available in only nine of 19 consultant units, and that in approximately seven units, mothers may have to wait up to 30 min for an anaesthetist to be available for an obstetric emergency. The authors point out the serious implications of lack of cover at consultant level; junior anaesthetists will not receive adequate training in obstetric anaesthesia, and neither midwives nor obstetricians will be educated to appreciate the benefits of modern obstetric anaesthesia.

This survey provoked an editorial on the subject (Reynolds, 1986). She has pointed out that similar problems exist in other regions and that obstetric anaesthesia may be occasional, unpredictable, urgent and difficult.

The existence of isolated maternity units without full back-up facilities and often without an experienced anaesthetist on site at all times can only be condemned, and every effort must be made to close such units, despite public opinion to the contrary. The small unit remains a liability (Reynolds, 1986). In addition to being responsible for the supply and maintenance of equipment and for all other facilities such as operating theatres and recovery rooms, the hospital authorities are responsible for ensuring that these specialist rooms are adequately staffed by appropriately trained personnel. Trained help for the anaesthetist must be available in all units, but is frequently absent (Mehta, 1981).

The second report from the Social Services Committee (Report, 1980) recommends that "health authorities should make every effort to provide an anaesthetic service that is available within a few minutes of receiving a call for *all* consultant obstetric units." The authorities are indeed being slow to implement these recommendations. Clearly, it is the responsibility of consultant anaesthetists to ensure that adequately trained anaesthetists are rostered to be immediately available for obstetric anaesthesia, but it is the health authorities' responsibility to ensure that such staff are available, with sufficient consultants to train them.

Obstetricians' responsibilities

Liaison between obstetricians and their anaesthetic colleagues has been criticized in more than one report. The main problem lies in the failure of obstetricians to give the anaesthetist appropriate time for adequate preoperative assessment. Sufficient time will allow institution of appropriate preventative measures in patients with pre-existing medical conditions. Such patients have often been in hospital for some time, and indeed the author was once given 30 minutes' notice of an impending Caesarean section in a patient with a prolonged Q–T syndrome who had been in hospital for the previous 16 weeks. There can be no excuse for lack of consultation concerning these patients, and failure to do so has contributed to maternal deaths.

Again, there is evidence of obstetricians imposing their will on junior anaesthetists to anaesthetize urgently patients having problems with which the junior staff were manifestly ill-equipped to deal in terms of knowledge, skill and experience. Nowadays, senior help is invariably available and early consultation will ensure the presence of a more experienced anaesthetist. It is to be hoped that such comments will disappear from the reports.

CONCLUSIONS

During the 30-year period so far covered by the Confidential Enquiries, maternal mortality has decreased by more than 90%, from 98.9 to 8.9 per 100000 total births, roughly halving in each decade. From table I, however, it would appear that no such reduction is occurring in deaths from anaesthesia, the percentage of true maternal deaths having gradually increased since 1952, although there has been a small decrease in the last reported triennium. At the moment, deaths from anaesthesia comprise 9.0 per million maternities or 12.2% of direct maternal deaths. Anaesthesia is the third commonest cause of death after hypertensive disease and pulmonary embolism. Such an outlook, however, is misleading, as what should be examined is the number of anaesthetic deaths in relation to the number of anaesthetics given, which includes extradural analgesia for pain relief. Such figures are not available, but it can be stated that there has been a marked increase in anaesthetic interventions in the past 10–15 years. Extradural analgesia became popular only in 1968. There were 1.4 million legal abortions, each requiring an anaesthetic, between 1968 and 1981, while the number of Caesarean sections has increased from 103 310 in 1970–1972 to 157 850 in 1979–1981. The actual number of deaths from anaesthesia has gradually decreased from 1970–72 to 1978–81. Using number of anaesthetics given as the denominator, there has been an enormous reduction in anaesthetic-related maternal mortality.

In 1970, Crawford drew attention to the anaesthetist's contribution to maternal mortality, basing his comments on the report for the years 1964–66 (Report, 1969). He concluded that the major share of the blame must lie with consultant anaesthetists for failing to ensure that appropriate standards were maintained. That his views have been heeded is indicated by the reduction in mortality that has been achieved.

The number of deaths is now very small and, under these circumstances, it is difficult to devise effective indices of quality control (Adams, 1983). Nevertheless, deaths still occur and it has been pointed out that a surprisingly common feature of mortality studies is that mishaps seem to occur, not from lack of knowledge, but rather from failure to apply such knowledge, from inattention or even from carelessness (Adams, 1983).

Lord Platt stated, in his 1967 Harveian oration "In the enthusiasm for teaching principles, the fact that much of medicine depends on the acquisition of technique is sometimes overlooked. Technique can be critical when academic knowledge is useless." These views are echoed by Dykes (1980) who stated "....current evidence, including that accumulating in our speciality, supports the importance of shifting from a knowledge-based to a performance-based educational and assessment system." In other words "It is sheer lack of skill that kills" (Rosen, 1984).

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HUMAN FACTORS IN ACCIDENTS

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At first sight, an article on human error based largely on military aviation accidents may appear to be inappropriate material for this Journal, particularly when it is written by one whose total knowledge of anaesthesia has been confined to two sessions in a dentist's chair; but a moment's reflection may show that errors in the air and errors in the operating theatre have much in common. Thus both pilots and doctors are carefully selected, highly trained professionals who are usually determined to maintain high standards, both externally and internally imposed, whilst performing difficult tasks in life-threatening environments. Both use high technology equipment and function as key members of a team of specialists, although not always with colleagues of their choosing, and are sometimes forced to operate at a time and under conditions which are far from ideal. Finally, they both exercise high level cognitive skills in a most complex domain about which much is known, but where much remains to be discovered; aeronautics, medicine, meteorology, pharmacology, etc. continue to be very active research areas.

Both pilots and doctors make many errors—that is, errors as defined by the strictest criterion of "performance which deviates from the ideal". However, the vast majority of the errors which they commit either are trivial or are easily rectified; thus an approach speed which is a knot or so too fast, or a poorly-worded communication, will probably dent only professional pride. Indeed, for all honest people, each day contains a a plethora of trivial errors such as forgetting to fill the kettle, stopping at a green light, or failing to notice the duplication of a word in this sentence. Usually there is sufficient slack in the system for the error to be ignored or noticed and corrected, but some apparently innocuous errors are not noticed and some systems are not so forgiving as others; for example, a high performance aircraft or a nuclear power plant will function through a host of complex interactions and be what engineers describe as "tightly coupled" (Perrow, 1984). That is to say that what happens in one part of the system directly, and often very quickly, affects other parts. Thus recovery from a control error when flying at high-speed, low level may not be possible, whereas the same error in the cruise might barely occasion comment. Therefore, for both pilot and doctor one of their frequent errors may, very occasionally, lead to a catastrophe or, in the often quoted words of Cherns, "An accident is an error with sad consequences" (Cherns, 1962).

Accident causation

Research into a number of accident areas such as aviation (McFarland, 1953; Wansbeek, 1969; Rolfe, 1972; Allnutt, 1976), nuclear power (Kemeney, 1979; Reason, 1986a) and maritime transport (Clingan, 1981; Wagenaar, 1986) shows that accidents are rarely produced by a single cause, but rather by a host of interacting ones—the proverbial "chapter of accidents". Indeed some investigators believe that looking for *the* cause of an accident is damaging (Holladay, 1973), while some organizations choose to distinguish between "primary" and "secondary" causes and some between "necessary" and "sufficient" ones (Wagenaar 1986). What is clear is that, whatever the categories used, many accidents are ascribed to "human error". In general aviation this figure varies between 42 and 87% (Feggetter, 1985), the figure tending to be higher for the simpler systems such as light aircraft. The term "human error," however, is often only a synonym for "pilot error", although the pilot may in fact be taking the blame for the real guilty party—the manager, trainer, aircraft designer or ground controller. So human error in the operating theatre *might* be the fault of the anaesthetist, but it might equally well be the fault of the person who failed to train him or her correctly or the person who failed to pass

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on a message, or who designed, bought, or authorized the purchase of, an inadequate piece of equipment. There is an extreme view which argues that *all* accidents result from human error and that those which we ascribe to "technical failure" or "act of God" merely reflect our ignorance or unwillingness to probe sufficiently deeply. However, for practical purposes let us merely say that accidents are usually complex and are caused, or at least exacerbated by, many factors and that human error often plays a large part in their causation.

An absolutely basic tenet of this paper is that *all* human beings, without any exception whatsoever, make errors and that such errors are a completely normal and necessary part of human cognitive function. For a pilot or doctor to accept that he or she is as likely as anyone else to make a catastrophic error *today* is the first step towards prevention; whereas to claim exemption on the grounds of being a test pilot, senior professor, commanding officer or consultant, or of having 30 years' experience or 3000 accident-free hours, is the first step on the road to disaster.

As hindsight is normally far superior to either foresight or insight, the most common starting point for a treatise on human error is the accident and its sequelae. This will lead us into a consideration of normal cognitive function and the operator's interaction with his or her colleagues (communication errors), equipment (machine-aided errors) and environment (environment-aided errors). While the examples quoted will be taken mainly from military aviation, the underlying mechanisms apply equally to cockpit and operating theatre and the reader is invited to supply his or her own examples. (Reports on individual military accidents have a restricted circulation and consequently are not cited in this paper.)

Accident investigation

From the moment that an aircraft crashes, or an accident occurs in the operating theatre, one of the two major sources of evidence starts to decay rapidly and to become distorted. This source is the memory of the participants, both direct and indirect, for the event. A large amount of laboratory and anecdotal evidence shows that memory decreases rapidly over time and that it is distorted in the direction of simplicity and coherence (Bartlett, 1932; Baddeley, 1976). We seem to hate informational chaos and to have a basic need to structure a situation and to provide a coherent account of what happened (Bartlett's "effort after meaning"). Thus, with the highest integrity, we soon start reporting not what happened, but *what must have happened*. Incidentally, the other major source of post-accident evidence (the physical factors such as the state of the aircraft engine, marks on the ground, documentation etc.) may or may not also be subject to decay, but this is outside the remit of this paper.

The primary tasks after an accident are of course to prevent further damage and to look after the injured; but second only to these is the need to facilitate the inquiry by minimizing the decay and distortions of memory (Allnutt, 1973). Thus all those who are involved in any way with the accident are encouraged to write down open-ended statements as soon as possible after the event (the statements are then impounded) and are advised, often unsuccessfully, to refrain from discussing the accident until interviewed by the professional investigators.

Military aviation accidents, in common with almost every other type of accident, are always a surprise and invariably occur at the most inopportune time and place. Nevertheless, a team consisting of two pilots, an engineer and a psychologist (plus other specialists if necessary) will try to get to the scene with all speed. They carry with them their luggage *and* their preconceptions; for as soon as the barest details of an accident are broadcast the cognoscenti immediately "know" what (must have) happened. ("That always was a dangerous manoevre"/ "I always said young Jones was an accident waiting to happen".) Even investigators will have their prejudices and theories; they may be overly sympathetic towards the pilot and they will make mistakes (even the psychologist!). In short, they will further distort the picture of what really happened.

The purpose of an accident investigation is to ascertain what happened and why it happened, so that systems and procedures can be improved (Rouse and Rouse, 1983), rather than to apportion blame, which may be dealt with by a subsequent inquiry. Such is the intent; but by their very nature accident inquiries are emotional occasions because families have been devastated, careers wrecked, etc. Investigators are human, and most would be happiest if the cause of the accident could be shown to be technical failure (human error at a distance) or freak weather conditions, but often there patently has been human error and the investigator may be exposed to the whole gamut of distortions of the truth ranging from the bare-faced lie to save one's own or a colleague's skin, through repression, to the witness being just a shade too selective in his account of events or letting a false nuance pass unchallenged.

The investigator must try to tease out the truth while taking great care not to lead the witness. An example of the care needed in the phrasing of questions is shown by Loftus's study in which subjects viewed a video film of a car crash and were then asked to estimate the car's speed at impact. The question asked of four matched groups of subjects was identical except for the verb used which was either "contacted", "hit", "collided" or "smashed". The subsequent estimates of speed correlated positively with the "violence" of the verb, ranging from 31 to 41 m.p.h. (Loftus and Palmer, 1974). Other problems with interviewer bias (Schmitt, 1976) and eye-witnesses (Wells and Loftus, 1983) must also be considered. At the end of this analysis the investigator may conclude that one of the factors which caused or exacerbated the accident was human error.

Cognitive function

The pilot of a modern military aircraft is bombarded by a plethora of information from his instruments, environment, co-pilot, ground control etc. He can only hope to process a small part of this input and his skill lies in simplifying the complex task by dealing correctly with the critical information at just the correct time. When he fails to do this an error, and possibly an accident, may occur. Although there is much current research and debate in psychology on some of the finer points of cognitive function, there is fairly widespread agreement on the basics of the system, as described for example by Wickens (1984) and Sanford (1985). First, the stimulus must fall within the range of the pilot's senses—that is, only a fairly narrow band of sound can be sensed and velocity can only be inferred. After sensation comes perception, for a stimulus does not fall onto a tabula rasa but rather onto a very active mind, and is rapidly converted into a meaningful percept. We then attend selectively to only a few of these percepts; the degree of attention varies and there is evidence to show that we process incoming stimuli to a variety of levels depending on many factors (Craik and Lockhart, 1972), but a simple binary division will suffice for this discussion of human error.

This simple division is between low-level processing where we appear to process very large amounts of information easily, very rapidly and in parallel, and higher-level processing which is the subject of conscious attention and in which we process information sequentially and comparatively slowly. The latter is William James' "window of consciousness" (James, 1890) and only a very small but most important part of our cognitive processing uses this mechanism. Failure of the low-level mechanism gives rise to *slips* and failure of the higher-level one to *mistakes*. We shall return to these two types of error shortly. Meanwhile, our cognitive processing system is completed by two main types of memory: a short-term "scratch-pad" where information decays in a few seconds and a long-term memory the contents of which will be distorted by both previous and subsequent events. (See Baddeley (1976) for a description of these and other types of memory.) Percepts and memories are then compared and decisions communicated to the effector mechanisms such as body movement and speech. Finally, feedback loops complete this very crude description of a hugely complex and highly sophisticated system.

Two types of error

The distinction between the two main types of error, slips and mistakes (Norman, 1980), is based on the failure of one or other of the two main processing mechanisms, fast low-level "schematic", parallel processing, or the slower high-level "attentional", sequential processing. We might note that some researchers (Rasmussen, 1981; Reason, 1986a) advocate a three-category system for errors based on failures of skill-based, rule-based and knowledge-based behaviour, but a binary split appears adequate for most purposes.

In order to cope with vast amounts of incoming information, and having only a relatively slow "attentional" processing mechanism, human beings have developed and built up a very large repertoire of "schemata". These are small routines (perhaps "sub-routine" would be an appropriate computer analogy) which are called into play by very specific stimuli and require minimal conscious monitoring. These schemata are accompanied by heuristics ("rules of thumb") based on what has worked well in the past and such mechanisms are essential if we are to function in this world of information overload. Thus our daily routine for getting up, washed, dressed, fed and to the office consists of a string of over-learned schemata to which we attend closely only when something disrupts our routine. When we are not paying sufficient attention an inappropriate schema may be "captured" or called into play and a slip occurs (Reason, 1986b). For example, a tired pilot landed on a hot day and intended to pull a lever to open the cockpit while he taxied across the airfield. At that moment he was distracted by a radio call which took his attention and he slipped into his post-take-off routine, pulling an adjacent lever which raised the undercarriage (or lowered the aircraft, as the pedants will insist). He realized his slip just too late and was heard to mutter the Naval synonym for "Oh bother"!

Diary studies (Reason and Mycielska, 1982) show how slips pervade everyday behaviour and are most likely to occur during the performance of highly automated tasks in familiar surroundings when attention is elsewhere because of boredom, preoccupation, or distraction. In particular, errors of omission are often caused by unexpected interruptions which may cause us to go back to a behavioural sequence at the wrong place. These slips are *not* arbitrary but tend to take fairly predictable forms (Norman, 1981). "When cognitive operations are under-specified they tend to default to contextually appropriate high frequency responses" (Reason, 1986b). This, as Reason acknowledges, is a derivation from the message of earlier authors such as the "false hypothesis" (Davis, 1958) and "response bias" (Broadbent, 1967). In short, when we don't have quite enough information we tend to go for what has worked in the past and we "see" what we expect to see and "hear" what we expect to hear.

A good demonstration of the tendency to default to a high-frequency response (or "frequency gambling") is the phonological priming game played by children. In this someone might be asked a rapid series of questions which provoke answers such as "most", "boast", "host", etc., and is then asked what is put into a toaster; he or she often defaults to "toast". As our expertise in a particular area increases, so does the problem of slips, for one way of defining an expert is someone who has built up a vast repertoire of appropriate and finely graded schemata which allows him or her to carry out many very complex procedures while devoting much of his or her attention to the "bigger issues". However, the penalty for this expertise is that the more schemata we possess, particularly subtle gradations of appropriate response, the more likely it is that the wrong schemata will be called into play when attention is elsewhere; that is to say, experts are, in general, *more* likely than novices to make slips. Some comfort may be drawn from Woods (1984) who showed that slips are detected far more often than mistakes.

Whilst *slips* are errors in which the intended action was correct but the actual action wrong, the second category of error, the *mistake*, is where the intention itself was wrong. Laboratory research and real-life observation indicate that human decision-making is often far from ideal and that we excel as pattern recognizers but not as calculators (Tversky and Kahneman, 1974). "Humans if given the choice would prefer to act as context-specific pattern recognizers rather than attempting to calculate or optimise" (Rouse, 1982). Having recognized the pattern or problem as analogous to one we have faced before, we quickly provide the first hypothesis which comes to mind and tend to stick with it, or "first come best preferred" (Reason, 1986a). If the hypothesis is correct, as it usually is, we enhance our reputation for decisiveness, but when it isn't we will often be very slow to change it. Again, both laboratory and observational evidence indicate that we prefer to seek confirmatory evidence rather than putting our hypothesis to a real test. The military accident literature contains many examples of pilots demonstrating this "confirmation bias" by making a navigational error and then "interpreting" a great deal of subsequent information to support their initial (erroneous) hypothesis. Similarly, as a slow-moving emergency develops, operators tend to take a "keyhole" approach, making a quick initial hypothesis and then jumping almost randomly from one focus of concern to another in an attempt to verify it (Reason, 1986c).

Communication errors

Many errors involve the team rather than the individual and, while monitoring another's performance may sometimes prevent errors from becoming accidents, the presence of others can provide a dangerous illusion of security as "divided responsibility is no responsibility". For example, an aircraft crashed into the Everglades while all three crew members were trying to solve a minor problem; and a British Airways 747 approached Nairobi airport for several minutes with none of the three crew reacting to the fact that the safety altitude had been set to 327 feet *below* ground level! (Aircraft Accident Report, 1975). Finally, an error may occur in the communication itself. The assumption is that as communication is about the same objective events it should be accurate, but communication is based not on the real objective world, but on our individual mental model of the world and the sender's and receiver's models may well differ significantly. Hence the much quoted, and probably apochryphal, accident caused by the pilot saying "feather four" meaning, on his understanding of the situation, "feather Number 4 engine" which was interpreted by the co-pilot, using his mental model of the situation, as "feather all four engines". History is replete with major communication blunders such as the Charge of the Light Brigade (see Reason and Mycielska (1982) for an interesting analysis of the errors), but a quick review of any day's conversations will show how people are "working from different maps". Nor must the importance of non-verbal communication be forgotten: mis-reading a gesture is a most common error.

Machine-aided errors

Well-designed equipment can prevent or at least ameliorate the effects of an error, whereas poorly designed equipment is often cited as the "cause" of an accident. What the pilot or doctor requires from his instruments is clear, concise, reliable, unambiguous information to the accuracy (but no more) which he needs; the controls must be comfortable, precise, easy to operate, unambiguous and give him immediate and adequate feedback that his intended action has been effected. To minimize errors and fatigue, displays and controls must be easy to use (by the pilot) while wearing full flying clothing and under the most severe environmental conditions. Not only must each display and control meet the design criteria, but they must be logically grouped together by function and information flow, with the most important being placed in the centre of vision. They must also obey the motion stereotypes (McCormick and Sanders, 1982); that is, we have all developed the schema that turning something clockwise increases it, while switches are down for "on" (opposite schemata in the U.S.A.). Above all, the system must be designed as far as practicable to save the operator from his own errors, for Murphy stalks the airways and the maintenance hanger (and, I suspect, the operating theatre). A $325 million B1 bomber was lost because the system allowed the pilot to cancel a warning signal without taking appropriate action (Cordes, 1985). Similarly, the gearbox of a military helicopter failed in flight because a maintenance technician read in the manual that "the thrust faces are mounted facing outwards": he assumed that this meant outwards from the engine whereas the writer meant outwards from each other. Thus an accident may well be the result of human error, but one committed many years before the event.

The advice given to a pilot who experiences a conflict between his body senses and his instruments is, "believe your instruments". This is almost invariably sound advice, but the problem comes when an instrument is known to be "sick" or when the information which it gives just cannot be fitted into any hypothesis which the operator can countenance. At one time during the Three Mile Island accident, the operators in the control room were faced with 114 simultaneous warnings and could not postulate an hypothesis to fit the data (Perrow, 1984). Ideally, an instrument should indicate if it is malfunctioning and the operator should have adequate procedures for continuing without it. This leads to the problem of reversionary mode procedures, for the more reliable the equipment the more "rusty" the back-up procedures and skills. The judgement about which reversionary mode procedures to train and maintain is a fine one, for there are some military flying procedures in which more people have crashed practising the reversionary procedure than following failure of the equipment itself.

There is now a strong case for arguing that there is no excuse whatsoever for poorly designed equipment and procedures in an environment in which human life is at stake. The principles of good ergonomic design have been known for several decades and are to be found in standard textbooks (Van Cott and Kincade, 1972; McCormick and Sanders, 1982). The most complex interface is between man and machine and this should be at the very centre of the design process. Various reasons are offered for poor design, such as ignorance of ergonomics, the belief that a good-looking (cosmetic) machine sells better than a safe one, or the fact that the equipment wasn't designed originally for the purpose for which it is now being used—for example military surplus equipment is often installed in light aircraft on the grounds of cheapness, but unpressurized aircraft do not require altimeters which read to 99 999 feet (Dale, 1985). Of course, the man–machine interface of the future will increasingly be a man–software rather than a man–hardware one, while the major focus of engineering psychology will continue to move from sensory motor concerns to cognitive ones (DeGreen, 1980). Although guidelines for the design of the man–computer interface exist (Smith and Aucella, 1982), they are often ignored and there sometimes appears to be an alarming trend back towards poor ergonomics; anyone who has sat in front of an expensive "user-hostile" computer which incessantly repeats "input error" will appreciate the concern.

Environment-aided errors

The role of stress in accident causation is a most complex one which usually leaves us at the end of the investigation with strong suspicion rather than proof. Consider, for example, a civil aviation accident in which a pilot was kept awake for most of one night because of a domestic dispute and then, after a 12-hour duty day, was faced with an engine failure just after take-off. The inquiry team opined that fatigue *may* well have influenced his decision to close down the good engine rather than the one which was malfunctioning; suspicion but not proof (CAP, 1969). Although there is not even an agreed definition of stress (authors talk about "stressors", "strain", etc.), the topic has spawned a vast literature of laboratory, field, observational and historical studies. The stresses themselves may be conveniently, although arbitrarily, divided into environmental stresses such as heat, noise, vibration etc., physiological ones such as sleep-loss, circadian rhythms, drugs, etc., and psychological ones such as fear, frustration, competition, etc. The literature has been comprehensively reviewed by, amongst many others, Appley and Trumbull (1967) and Poulton (1971).

Of the many things which may be said about stress and human error, six simplistic generalizations may suffice. These are:

(a) Most research has been into the effects of single stresses, whilst real-life environments contain many stresses, the effects of which depend on a host of intervening variables such as the fitness, training and motivation of the operator, the nature and complexity of the task and the strength, duration, interactions and suddeness of onset of the stresses involved.

(b) Objective and subjective reactions to stress are often not well correlated. Thus the real danger of alcohol is not that it degrades performance, but that it does so whilst we think our performance is good (Cohen, 1960). A related problem with alcohol is that pilots do not appreciate the duration of its effects and often feel safe just because it is a new day (Green, 1983). It is also impossible to divorce domestic from work stresses, and domestic stress has been shown to increase proneness to accidents (Rahe, 1969; Alkov, Borowsky and Gaynor, 1983). Thus a real menace is the very senior man who claims to "leave my worries behind me when I enter the cockpit" or to have "trained myself to do without sleep". He has not, but his juniors may be just a shade reluctant to point out to him the relevant psychological literature!

(c) The break-down of performance under stress may take many forms, such as increased errors and irritability or decreased speed and accuracy, or both. Two mechanisms seem to feature in accident investigations with particular frequency. One is what is commonly referred to as "coning of attention"—that is, at a time when we most need to gather a broad spectrum of data in order to make a good decision, we concentrate on one single source, the "first come, best preferred" solution described earlier. An extreme manifestation of this phenomenon is when passengers in a crashed aircraft struggle to open a door while ignoring a large hole in the fuselage a few feet away. The second mechanism is "reversion under stress". Man cannot make himself forget and both laboratory and observational evidence shows that, under stress, recently-learned behaviour patterns may be replaced by older, better-learned ones (Fisher, 1984). Thus a small explosion on landing caused a military aircraft to veer off a runway and down a hill with the pilot furiously trying to stop it with the hand-brake. Sadly, that type of aircraft was not fitted with a hand-brake, but the aircraft which the pilot had flown for the previous 6 years had been so fitted.

(d) In general, performance seems to follow an inverted U-curve, being best at moderate levels of arousal (Yerkes and Dodson, 1908) or in the middle of the "day-dream to panic" continuum (Lager, 1973). This produces two danger points: boredom and panic. In the former, arousal is very low, attention elsewhere, and slips occur; in the latter, the "chapter of accidents" builds up inexorably until the pilot is overwhelmed and mistakes (and slips) occur.

(e) Manhood and safety may appear to be incompatible. Our culture, particularly in activities such as flying and sport, endorses concepts such as "manhood" and "pressonitis" and looks a little askance at an over-concern with safety (Mason, 1972); but this same phenomenon also appears in a much more subtle form and among many groups of professionals there is often a marked reluctance to "lose face" by admitting ignorance or fatigue and handing over to a colleague who may be more able, less fatigued and, perhaps, junior.

(f) Money and safety often appear to be pulling in opposite directions. A pilot is not employed "to fly safely", but "to fly, safely". He is there to win the war or to make a profit for his company and to do so safely. Thus safety would be enhanced enormously by not flying in bad weather, but profits would suffer and so the whole question becomes one of "acceptable risk"; for example, 31 of the 40 pilots who first flew the U.S. Mail died in flying accidents (Perrow, 1984). It must be remembered that we are talking here about both "perceived risk" and "actuarial risk". The helicopter pilot who crashed in the mountains trying to rescue what he believed to be a badly injured man based his decision on his assessment of the risk; that the man was not in fact badly injured is irrelevant to our judgement of his decision.

Future errors

As our knowledge of human cognitive processes gradually improves we see that man's cognitive capacity is the fixed element in the system and that slips and mistakes are natural, ubiquitous behaviour occasioned by various combinations of cognitive, social and situational factors. Although we cannot predict when and where the next accident will occur, we can predict with confidence that human error accidents will continue unabated and indicate situations in which they will be more likely to occur. The key issue is whether the number of such accidents can be reduced in the future.

In some senses the situation is steadily deteriorating as man is called upon to undertake ever more challenging tasks and the potential consequences of human error in highly sophisticated, tightly-coupled systems, such as high speed aircraft and nuclear power stations (such as Chernobyl), are catastrophic. However, there are at least three reasons for optimism. The first is that much of the information necessary for the design of good "man-compatible" equipment and procedures is readily available; the missing element is the willingness to apply it. Second, while it may sound like a pious hope to expect that a better understanding of human attitudes and behaviour, particulary in a crisis, may diminish the chances of an accident, there are some encouraging signs in this direction. Many military organizations are now adopting a much more sensible attitude towards human error and are investigating ways of identifying pilots who are more likely to have accidents; various agencies, including some armed forces, are starting to use relaxation training to counter stress and one of the recommendations of the Three Mile Island enquiry was that an incident monitor should sit quietly in an isolated room away from the trouble-shooting team and think about the incident as a whole (Perrow, 1984).

The third reason for optimism could in the end prove to be the most rewarding. This is the hope that a very real symbiosis between man and machine could allow each to counter the other's weaknesses. Such a productive partnership may seem very far off to those of us whose "partnership" with a personal computer seems to produce an even greater mess than we might have achieved single-handed, but the potential is there because man possesses attributes such as drive, intuition and pattern-matching skills etc., while machines are dispassionate, possess reliable and virtually unlimited memory and never tire of repetition. Work on Expert Systems, while proceeding in more of an evolutionary rather than the revolutionary manner which some had expected, is progressing. In particular, Intelligent Decision Aids (Rouse and Rouse, 1983) will be, and indeed are beginning to be, programmed to respond to the particular needs of the individual operator and to "understand" how he functions. They will collate a plethora of incoming information, make inferences and offer a decision to the operator together with information about the basis on which it was made and the probability of its being correct.

Technology marches on apace while human cognitive processes and capacity have remained remarkably stable over the centuries. Systems and procedures designed around a thorough knowledge of human cognition and attitudes have the potential to prevent, or ameliorate, some of the errors which are a normal and necessary part of human functioning. There are some encouraging signs that our attitude towards human error is improving, but it is likely to be some considerable time before the operator, be he pilot or doctor, ceases to be the first choice for "guilty party"; hence the definition of a pilot as "the person who attends the accident".

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NO FAULT COMPENSATION FOR PERSONAL INJURY IN NEW ZEALAND: SOME IMPLICATIONS FOR ANAESTHETISTS

J. M. GIBBS

New Zealand has a long tradition of legislation designed to reduce the personal impact of illness and accident. A comprehensive government-funded Health Service has functioned since 1935. In 1966, a Royal Commission headed by a Judge of the New Zealand Supreme Court was appointed to examine problems faced by the community in coping with the immediate and more remote consequences of personal injury (Woodhouse, 1967). The Commission's report made recommendations arising from "the inevitability of two fundamental principles":

> No satisfactory system of injury insurance can be organized except on a basis of community responsibility.
>
> Wisdom, logic and justice all require that every citizen who is injured must be included and equal losses must be given equal treatment. There must be comprehensive entitlement.

Arising from the report of the Royal Commission, an Accident Compensation Commission (ACC) was established to commence activity in 1974. Until that time, the law in New Zealand related to personal injury was very fragmented. Accident or disease which could be shown to be work-related might be compensated from compulsory insurance held by the employer. Criminally- and motor vehicle-induced injury were also associated with specific compensation schemes. In the medical sphere it was possible to obtain damages if negligence on the part of some other person could be established.

Before looking at the consequences of abolition of these sources of compensation, it is necessary to review principles related to a common law action for negligence as these were applied in New Zealand until 1974. The critical issue was not the outcome of the accident, but whether or not the defendant was at fault. If no fault was proven then the plaintiff was left to bear the burden. Liability was determined "not by the quality of the defendant's conduct, but by its results". In favour of the right to bring a common law action for negligence, it has been stated that the threat of damages gives a financial incentive for care on the part of the person providing it. The Royal Commission considered that this threat loses force against the background of insurance leading to widespread sharing of any risks. It also considered that there were worldwide reports of unfair decisions reached in common law actions.

The special topic of injury arising from medical treatment was not discussed by the Royal Commission in any depth. Such injury was included in the scheme because the victim has suffered personal injury "no matter where or how the injury might occur".

The Royal Commission recommended that the law relating to personal injury in New Zealand should change in a number of ways:

> "That the procedures and techniques of private litigation be replaced by non contentious processes of assessment and review with recourse to the courts only on a point of law."
>
> "That if the scheme is to be universal in scope, it must be compulsory in application. Accordingly, there will be no place for special arrangements for contracting out."

The major recommendations of the Royal Commission were embodied in legislation which took effect on April 1, 1974. After that date a person suffering injury by accident had no *civil* right of action against any other person either at common law or under any statute. The provisions

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of the Accident Compensation Act provided the only avenue for recompense. The original act was redrafted in 1982 when the Accident Compensation Corporation replaced the earlier Commission.

Under the definitions of personal injuries by accident "medical, surgical, dental or first aid misadventure" is included, while damage from cardiovascular or cerebrovascular episodes is ordinarily excluded. Many of the consequences of the definitions used in the legislation have been carefully reviewed by Blair (1983). He notes that in New Zealand law the term "misadventure" has not been previously used. He considers it is implicit that legislators intended that "medical accidents" should have the protection of the Act. Importantly, "medical misadventure" has a wider meaning than "medical negligence". In discussion on this issue, Blair cites the case of Roe *v.* Minister of Health (Cope, 1954) in which permanent neurological damage occurred after the subarachnoid administration of "tainted anaesthetic injections". It was considered likely that there were "invisible" cracks in the ampoules but, because there was no reason to foresee that the ampoules were cracked, there was no negligence. On the same facts, the plaintiffs would have had a valid claim under the New Zealand Accident Compensation Act. There are now no grounds for a common law claim for negligence against a medical practitioner. Any such claim could be dealt with under the broader heading of medical misadventure. If the Corporation accepts a claim it becomes liable for payment in respect of the victim's reasonable medical costs as submitted by registered practitioners and costs for matters associated with that treatment and with the results of the accident. There is also provision for lump-sum payments in the event of permanent bodily impairment, suffering, loss of amenities, disfigurement or neurosis.

When an accident has occurred there must be notification of the fact and circumstances to the Corporation, together with supporting medical and other reports as required. Details of functioning in terms of payment procedures are outside the scope of this paper. However, in outline, the Corporation considers the evidence available to it and then gives a decision in respect of payments to be made and associated administrative matters. If there is dispute as to fact or in respect of the degree to which injury by accident may have contributed to the patient's state, there is provision for review, initially within the Corporation.

This gives the Corporation a quasi-judicial function. It has the power to summon witnesses, administer oaths and hear evidence in the manner of a Commission of enquiry established by the Crown. However, the adversary system used in courts of law is not a part of review hearings by the Corporation. Claimants have the right of appeal from decisions of the Corporation or a Review Officer to the Appeal Authority (established under the ACC Act) and from thence to the High Court on a question of law or of general or public importance. Cases may ultimately reach the Court of Appeal on a point of law.

Medico-legal aspects

Medical Misadventure is frequently the subject of review proceedings. This has led to a more detailed interpretation of the meaning of the term for the purposes of the Corporation (ACC Report, 1978, 1985). There are areas here of considerable relevance to anaesthetists.

Medical Misadventure occurs when:

(a) A person suffers bodily or mental injury or damage in the course of and as part of, the administering to that person of medical aid, care or attention.

(b) Such injury or damage is caused by mischance or accident, unexpected and undesigned, in the nature of Medical Error or Medical Mishap.

These latter terms require a measure of amplification.

Medical Error. The failure of a person involved in the administering of medical aid, care or attention to observe a standard of care and skill reasonably to be expected in the circumstances. There cannot be a claim for medical error just because hoped for results are not achieved. Thus if a patient suffered a hypersensitivity reaction to an anaesthetic drug, the anaesthetist would not ordinarily have erred (although the event may allow for a valid claim as a Medical Mishap). If the patient had been previously identified as reacting adversely to that drug, then there would be a case for a finding of Medical Error.

Medical Mishap. This covers the situation where an unexpected and undesigned incident, event or circumstance of a medical nature having harmful consequence to the patient intrudes upon the administering of medical aid, care or attention. It might be felt that the anaesthetist's damaging a tooth during laryngoscopy constitutes such an event. However, in recent years the Corporation has rejected claims on the grounds that such damage is not "beyond the range of adverse circumstances normally and reasonably contemplated as within the risks attaching to the administration of such aid, care or attention...".

To gain an indication of the number and effect of rulings by the Corporation which have been directed at anaesthetists, an approach was made to a senior medical officer in the Corporation who is an anaesthetist. The Corporation does not classify its files by specialty, so that national figures were not obtainable. However, the office surveyed handles some 20% of all claims. The period surveyed covers from 1979 to the present. Claims (10) in respect of hypersensitivity reactions to anaesthetic drugs were all accepted as medical mishaps. The same was true of claims for halothane-associated hepatitis (three), malignant hyperpyrexia, neostigmine-induced bradycardia with fatal cardiac arrest, renal failure after repeated methoxyflurane inhalation and severe bronchospasm in a known asthmatic after tracheal tube placement. Claims such as these resulted in financial recompense to the patients or dependents, but it must be stressed that even if there was blame attached to the anaesthetist, this was not considered relevant to the compensation given.

A few cases involving anaesthetists have come to appeal hearings (ACC Appeal Authority, 1984). For example, in an operative procedure to remove skin and redundant tissue from the region of the elbows, anaesthesia was administered with neuromuscular blockade, nitrous oxide and oxygen (2:1 mixture), together with increments of droperidol, fentanyl and diazepam. It subsequently transpired that the patient was aware of events during the procedure, including pain in the area of operation. A claim for compensation on the grounds of medical misadventure was declined at initial hearing and an application made for review. The review officer cited the definitions of medical misadventure given earlier in this paper and then went on to note the concern of the plaintiff that members of the operating team and her family would not accept her story. Evidence as to the occurrence of awareness was produced, convincing the review officer of the reality of the plaintiff's experience. However, because of that literature evidence, the Appeal Authority held that:

"In order that a claim for medical misadventure can be established on grounds other than medical negligence or error, it must be shown that the consequences were rare or of an adverse nature. In view of the articles referred to which are very extensive, I am satisfied that the awareness suffered by the plaintiff was not a rare or adverse consequence of the proper medical treatment she was undertaking and accordingly I must agree with the decision reached by the review officer."

Perhaps surprisingly, this decision was not appealed. It emphasizes that, even with a change in the nature of the legal process, there is potential for differences of opinion as to whether or not all plaintiffs are fairly treated. It could be realistically compared with a recent British decision in respect of awareness during anaesthesia (Brahams, 1986) when a similar claim was successful.

New Zealand has not been immune to the increases in consumerism which have greatly influenced patterns of life in developed countries. Thus we have been faced with a community which no longer accepts the advice and actions of the medical (or any other) profession without question. In parallel with scientific and technological advances in medicine, there have been demands for the delivery of a product which fulfils the expectations held of it. In anaesthesia a patient may have concerns about certain aspects of his or her anaesthetic, but expects to come through the experience with no adverse consequences relevant directly or indirectly to the conduct of anaesthesia. If there is some adverse experience, then all too often there will be questions raised as to the blame which may be attached to the anaesthetist in respect of those events. In New Zealand, no longer can an action be brought under common law—with all its punitive connotations. Many senior legal and medical practitioners consider that this change in the law, notwithstanding the financial protection (modest in amount) available through the Accident Compensation Corporation, has led to the significant increase in complaints to the Medical Council of New Zealand and to the Medical Practitioners Disciplinary Committee (MPDC) of the New Zealand Medical Association.

The Secretary of the MPDC noted that, in 1970–74, the Committee received an average of 10 written complaints each year. From 1980 to 1985 the number had reached 130 each year. During this latter period, one complaint against an anaesthetist was considered sufficiently serious to warrant a finding of professional misconduct. This was the case involving suxamethonium administration despite the existence of documented hypersensitivity to that drug referred to earlier. It is the view of the secretary of the MPDC as well as that of lawyers acting on behalf of the Medical Defence Union and the Medical Protection Society that doctors will come under more intense scrutiny in respect of their actions in part because of the removal of the "safety valve" of the right to sue for negligence.

Criminal proceedings can still, under the Crimes Act (1961), be brought against medical practitioners "who fail without reasonable excuse to discharge their duty to use reasonable knowledge, care and skill in carrying out treatment, the doing of which may be dangerous to health". Such a charge would not be laid unless the negligence or conduct alleged is of a gross nature. The author is aware of several cases involving anaesthetists in which police enquiry has led to a soliciting of opinion from senior anaesthetists as to their views in respect of an anaesthetic-associated death. In one of these, charges of manslaughter were laid. The case involved a 10-year-old boy with acute appendicitis. A senior locum anaesthetist who had not previously used the anaesthetic machine in question inadvertently gave a gas mixture containing carbon dioxide and nitrous oxide, by confusing the position of the rotameter control knobs. The mistake was first detected when the surgeon reported dark blood in the surgical incision. It seems likely that a nurse drew attention to the bobbins of the rotameters. There was much medical and other evidence on the responsibility of the hospital to have instructed the anaesthetist as to the presence of carbon dioxide and about the equipment to be used. There was conflict on responsibility for the management of the patient after the cardiac arrest had been corrected. The patient died as a result of cerebral hypoxia 30 h after the accident. A verdict of guilty was returned and the anaesthetist fined the sum of $4000. The author was not involved with the testimony, but did sit through much of the proceedings. In my view it is doubtful that the events of seconds or minutes can retrospectively be reconstructed after many months in a way which allows the actions of the individuals concerned to be placed in proper perspective. The fact that gross mistakes were made cannot be in question, but many have been profoundly troubled as to whether these rendered the anaesthetist—acting in profound error but in good faith—guilty of criminal behaviour. It should again be pointed out that the patient's relatives had no right to sue for negligence in a civil action. It must be further noted that because of the nature of their work, the mistakes made by anaesthetists tend to be obvious in a "cause and effect" manner, whereas those of other doctors—for example, mistakes related to inappropriate drug therapy—may be less apparent because of delays in the appearance of an adverse consequence. This makes anaesthetists a vulnerable group, as reflected in the incidents reported in this paper or in the generally high medical malpractice insurance premiums for anaesthetists in the United States.

For the majority of patients, the workings of the "no fault" accident compensation scheme in New Zealand have given an immediacy and certainty to earnings-related protection, so the scheme has worked to their considerable advantage. For anaesthetists, as for other medical practitioners, the scheme, together with increased questioning of their actions, has increased responsibility for careful practice along accepted lines. A corollary to this must include the need for proper records and for very full documentation of any adverse circumstances.

SUMMARY

In recent years, there has been an increase in medico-legal and disciplinary actions against doctors, some involving anaesthetists. While this has occurred at a time of increasing questioning of doctors' decisions, in New Zealand there has been the added dimension of a major change in the law related to personal injury. Under the provisions of the Accident Compensation Act there are no grounds for a civil action against a doctor in respect of a medical misadventure. The only provision for recompense is through the Accident Compensation Corporation. With the removal of the punitive aspect of civil actions against doctors, there has been an increase in complaints through other channels. The anaesthetist is particularly vulnerable because of the immediacy with which an adverse event is likely to cause obvious harm to a patient. This can only be countered by high standards of practice, together with careful record keeping.

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LEGAL OBLIGATIONS AND RESPONSIBILITIES OF THE MEDICAL PRACTITIONER

J. D. FINCH

The purpose of this article is to present a brief review of legal basics as they affect medical practice.

To many medical practitioners the law seems a threat. The law, as practised by lawyers who are its professional operators, may easily be seen as a threat to clinical independence and autonomy. It therefore comes to be seen as an undesirable activity which should keep to its own province and leave the professionals alone.

What may the law or lawyers say usefully about the professional and expert responsibilities which are the very essence of the job of the trained and skilled anaesthetist? Is it necessary to conduct anaesthetic practice, and indeed medical practice generally, in a defensive manner?

These are important questions. They are particularly pressing at a time when subscriptions to the defence societies are increasing at a tremendous rate. The newspapers and the journals seem to be publishing an increasing number of accounts of damages and awards made against professionals, those assisting them, and (if relevant) the employing Health Authorities. This is occurring at a time when techniques and technology are advancing at such a rate as to place upon the professional an ever-increasing burden in respect of maintenance of knowledge and standards. To quote the words of former Master of the Rolls, Lord Denning, in a statement applicable to this field of professional responsibility: "It is all very worrying".

It is not surprising, therefore, that the law appears directly in the guise of an advancing threat. Ironically, and disturbingly, this threat appears to increase in direct proportion to advances in techniques and technology and in corresponding patient care.

As the training of medical professionals makes increasing demands on time, both of those who train and those who receive such training, a corresponding decrease may occur in the provision of opportunities to study aspects of practice or future practice other than those which are purely clinical. A considerable effort therefore needs to be made (and in a number of schools is being made) to incorporate to medical education and training certain broader aspects of practice aimed at producing more rounded and better informed practitioners. This includes primarily social and psychological aspects to the practitioner's role.

What is frequently forgotten by anaesthetists is that the broadest (and in many senses the most important) contextual aspect to medical practice consists of the legal parameters of the great responsibilities which are exercised. The legal context of the exercise of responsibilities and duties both limits and enables. This information is a vital clue in answering whether or not the law is, or is not, seeking to interfere with professional and clinical responsibility. The law limits, because it says that certain things may not be done or will not be tolerated. It does this by both the criminal law and the civil law. The criminal law consists of rules imposing penalties, while the civil law consists of principles of compensation. Concepts of fault are common to both aspects, although they work differently.

On the other hand, the law enables. In setting down limitations and restrictions on what is to be permitted or tolerated, the law is creating a broad framework and a framework alone. Once the broad parameters of duty and responsibility are set down, either by statute or regulations, or more usually by the common law (see below), the law leaves well alone. Where the law stops, professional and clinical judgement and responsibility begin.

Thus the law affecting the exercise of professional responsibility and judgement is a para-

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mount factor in medical practice. Its particular stipulations and prohibitions may change from time to time, not least in response to advances or changes in clinical practice itself, but its prohibiting and enabling force is permanent.

Why is it important for practitioners and would-be practitioners to have a "feel" for the law which affects their practice? What is the point, it may be asked, of knowing anything about the law if professional responsibility is exercised with care and in good faith? If practitioners act for all their professional lives in a manner which is both professionally and legally acceptable, what possible advantage is there in the slightest knowledge of the broadly-set legal duties which have always been complied with?

One response may be to say that a knowledge of the law affecting professional medical practice is a luxury which only time taken out of patient care and research will allow to be indulged. Molière's character in *Le Bourgeois Gentilhomme*, Monsieur Jourdain, was distinguished for his ability to speak prose without knowing it! If professional medical compliance with what happen to be the vital legal parameters of practice were in reality to be nothing more distinguished than Monsieur Jourdain's mundane gift, a specific study of legal aspects of professional medical practice would be trivial and probably worthless.

However, there is a world of difference between the mundane and the professionally responsible. Professionalism, it is argued, carries with it both the moral and practical responsibilities of knowing the limits of the law. To know those limits is to know those situations where the law reserves the right to condemn a clinical practice as wrong. Equally, to know in broad terms the restrictions which the law lays claim to impose on clinical practice is to see in sharp relief the genuine freedom with which professional autonomy and clinical judgement can be exercised.

It is therefore with an eye to both the enabling and the restricting objectives of legal regulation of medical practice that the following introduction to legal basics is offered.

DUTIES OF CARE AND THE CONCEPT OF NEGLIGENCE

A familiar beginning to any discussion of legal aspects of professional medical responsibility is the apparently unpleasant topic of negligence. The concept of negligence in the law of the United Kingdom includes three essential elements: duty of care; breach of that duty; damage, harm or injury resulting from that breach. These three elements will be discussed and their particular relevance to the practice of anaesthesia and to medical practice in general indicated.

"Duty of Care"

If two people enter into a contractual agreement, the duties which each owes the other may be reasonably clear. They may be expressed, or they may be implied. At all events, the parties to the agreement have had a direct say in the consequences of what they have arranged, and thenceforth in the legal relationship which is to exist between them until such time as the duties and responsibilities consequent upon their agreement are fulfilled or discharged. While a careless regard to contractual obligations may lead to damages for breach of contract, carelessness in the "full-blown" sense of Negligence can exist in its own right. Negligence forms an integral and vitally important part of the law of tort. The word "tort" is (in common with other legal words) derived from the original Norman French. In French, the word simply means "wrong", but the law has to be more specific these days than merely telling someone that they have done wrong. Another source of common legal words and expressions is Latin, and it is from the Latin that the word "trespass" is derived. Trespass is a corrupted derivation of the original "transgressio". To transgress is to do wrong, although the law of trespass is (as will be explained) much more complex these days. In *The Lord's Prayer*, requesting forgiveness for trespasses (normally) goes wider than merely seeking indulgence for having walked across one's neighbour's garden. So, in order to establish a case of negligence, all the elements of that tort have to be proved. The first element, duty of care, gives rise to relatively little difficulty. Certain comments, however, ought to be made which distinguish the duty in tort from a duty in contract.

It is a commonplace to say that a caring relationship exists between a practitioner and a patient. The duty to take care is in a broad sense a professional and ethical duty. It consists in part in a duty to do things in a caring way, but the law is, and has to be, more specific than this. The concept "duty of care" is in essence a link by means of which a necessary legal connection is established between the parties to a relationship, in this case doctor and patient. So far as concerns the law of contract, people make that link between themselves and by themselves, and the law attaches certain consequences to what they have done. The legal relationship between medical practitioner and patient in the independent health care sector is a contractual relationship. Expressed, or more usually implied, terms of the relationship into which they have entered will form the basis for the resolution of any dispute between them and, even in the absence of a dispute, the basis of the differing responsibilities which each owes the other (in simple terms, in the duty to treat, and the duty to pay for the treatment).

An implied term of any contractual relationship for the delivery of personal health care is that such delivery will be pursued with proper caution and with an eye to the avoidance of harm. The duty of care in tort, which forms this first vital element of the law of negligence in the law of tort, can normally be formulated in much the same way. So why make the distinction between tort and contract in this regard?

The difference can be explained by distinguishing between a duty to take care in treatment which aims towards cure, and a duty which is undertaken to effect a cure. So far as the latter is concerned, there is nothing in law to prevent a practitioner from undertaking by way of contract to guarantee a specific result. It may well be an unwise practitioner who would do this, but that is the way the law stands at any rate. On the other hand, so far as the avoidance of negligence in tort is concerned, the duty never approaches an obligation to effect a cure or to effect a particular result in the health or physical condition of the patient.

The difference in incidence of duties in tort and contract may be illustrated by a story from the United States. One day, a businessman was playing golf with a friend of his who was a plastic surgeon. Their conversation ranged from this to that, and at one stage happened on the subject of skin. The businessman told his golfing friend that his son had for some time been suffering from an acute but increasingly chronic condition of the skin on the palm of his right hand. The surgeon, who happened to be an expert in such matters, undertook to see the boy at a private consultation. Following observations made at this consultation, and tests following it, he felt so confident at the prospective exercise of his own clinical abilities that he told the businessman "I will guarantee the cure of your son's skin condition".

An operation followed during which skin was grafted from the boy's chest to the palm of his right hand. The skin graft took exceedingly well, and both boy and businessman father were delighted. A substantial sum of money changed hands, and seemed well worth the cost. When the boy reached puberty, however, things took a wrong turn. The chest hair which began to show signs of growth on the boy showed signs of growth also on the palm of his right hand. Neither boy nor father found this turn of events amusing; they sued the surgeon, and won substantial damages against him.

In this example, the obligation which the surgeon undertook was an obligation to effect a cure. Had his obligation been not to effect a result, but simply to aim by the exercise of reasonable care at a given desirable result, the situation would have been entirely different. The boy's action would have failed.

The duty of care, therefore, serves as a legal concept by which to tie together, or form obligations between (Latin "ligare", to tie or bind) those whose legal relationship the law is scrutinizing. So, far from interfering with a clinical or therapeutic relationship, the law is, at this point in the formulation of its concept of legal obligations between doctor and patient, simply making more specific, and with a specific aim in view, that which is already obvious in point of fact.

DUTY OF CARE AND STANDARD OF CARE

Discussion sometimes takes place, even in legal textbooks and in the decisions arrived at by judges in the determination of disputes in court, on "high" and "low" duties of care. These references are potentially highly misleading. Duty of care is neither high, nor low. It is a linking concept, as explained above. On the other hand, what may be high or low is the *standard* of care which the legal relationship between the parties (established by the concept of duty) envisages as suitable to discharge the obligations following from that relationship.

It is therefore with the concept of "standard of care" that we deal next, and centrally in this brief survey of legal aspects of practice. It is in the context of a discussion of standards of care in medical, and indeed any professional practice, that the suspicion may arise of legal interference with professional autonomy. It is hoped that the following explanation may help to dispel this common suspicion.

The standard of care expected by the law of medical practitioners in general and of anaesthetists in particular is the standard reasonably to be expected of a skilled and competent practitioner of that art. It is not, on the one hand, the standard which happens to be observed by any single member of the particular discipline involved. That would have the obvious consequence of putting any given medical practice outside the law. Nor, on the other hand, does the law formulate its demand in terms of the best or something which aims at the best. It is precisely here that a vital distinction has to be made; that distinction should be made between the obligation of basic duty, and the obligation (or professional ethic) of aspiring towards excellence in practice.

The law does not demand excellence. It demands competence. A famous formulation of the standard of care expected of ordinary people in doing ordinary things consists in the invocation of the "man on the Clapham omnibus". The man on the Clapham omnibus has alternatively been portrayed as "the man who reads the magazines at home and pushes the lawnmower in his shirt-sleeves". He is distinguished by his lack of distinction; he is a very ordinary person. Medical practitioners, by contrast, are not distinguished by their "ordinariness". They are distinguished by their professional education and training, by a particular skill and competence, and by the pursuit of a particular professional ethic. How "special" does the law then make the standard of care which they have to display if they are to avoid an accusation of negligence? It is precisely here that the law has to be, and indeed is, immensely careful to steer an acceptable middle course between interference with properly exercised clinical autonomy and, by contrast, casting the broad parameters of professional legal responsibility to the wind.

It is essential at the outset to realize that it is not the law, indeed lawyers, who are "interfering" when any criticism is offered of a given medical practice which becomes the subject of a dispute. It is here that a vital distinction has to be drawn between the objectives of the criminal law and those of the civil law of compensation.

No-one is an expert in fulfilling the obligations laid down by the criminal law. Either a crime has been committed by a given action, or it has not, and there is an end to the matter. True, judicial interpretations especially at Appeal Court level have to be made of the many refinements which are required of basic concepts of the criminal law, but the core of criminality is certain, and requires no expert intervention to demonstrate it.

While expert opinion is, or should be, irrelevant to the question of fact whether a crime has or has not been committed, expert medical opinion is of the very essence when it comes to considering questions in tort as to the requisite standard of care. Once the initial link of duty of care has been established between practitioner and patient, the standards incident to that duty become a proper matter of scrutiny both for the profession itself and for the law. Most disputed cases never reach the court stage; they are either settled or dropped before that stage is reached. Nevertheless, the attitudes demonstrated by courts in the handling of disputes involving medical liability and responsibility are guides to the nature and extent of obligations inherent in situations which never reach that much-feared litigation.

THE ROLE OF THE MEDICAL EXPERT WITNESS

The setting of acceptable standards for any profession, be it medical or otherwise, could never be left to that profession alone to the exclusion of any other criterion. To allow that to happen would, both logically and practically, be to put the activities of that profession beyond the reach of legal regulation or legal cognisance. On reflection, that would not be a Utopia, but its very antithesis. This introduces the concepts of the medical expert witness in questions of the fulfilment or otherwise of standards of medical care rightly accepted as proper by a substantial body of professional opinion.

Medical expert witnesses are special. Witnesses in "ordinary" cases relate to fact alone. For instance, a witness called to give evidence in the case of an ordinary traffic accident action could be a witness as to the vehicle's estimated speed, or as to the state of its brakes, or as to any other relevant fact. That witness might have opinions as to whether the speed, vehicle condition, etc., were evidence of negligence and of an insufficient standard of care. Be that as it may, such opinion would be immaterial to the business before the court. Medical expert witnesses are witnesses to something more than bare facts. They are called precisely in order to express a considered, expert and therefore respected professional opinion on the matter in hand. Such, for instance, would be an opinion not just as to whether or not such and such a doctor did such and such an act, but whether or not that act displayed a standard of care, skill or competence professionally accepted as proper within the relevant branch of practice. More than one medical expert witness may be called by the same side to a dispute in order to testify as to the same or an associated question of acceptable standards of care and practice.

On the basis of hearing medical expert evidence for both sides to a dispute in court, it is the judges' task to "determine" the dispute in hand. Pity though it might seem in some cases, a judge in court cannot simply pull his wig back over his head and tell all parties concerned that he has had a fascinating day listening to both sides and prefers not to rule in favour of one side or the other. Practising and academic lawyers have a habit of referring to the ending of disputes by way of the word "solution". On reflection, the decision one way or the other may be anything but a solution to the losing side. It may, indeed, be the very beginning of professional and financial problems which have in turn to be resolved.

The term "determination" is more realistic to describe the type of situation which arises when even medical experts disagree on the acceptability of the practice.

To this explanation there is, however, one immensely important caveat. This consists in the principle, long enshrined in general terms in the common law but specifically delineated in the 1983 House of Lords decision in the case of Maynard *v.* West Midlands Regional Health Authority, that adherence to a particular school of thought is, in itself, no basis for a finding of negligence merely because other schools of thought or practices are testified to as acceptable by medical expert witnesses for the opposing side. The necessity for the existence of such a principle is of course obvious. To put the matter in what is probably a quite inapposite way, there is more than one way to skin a rabbit. Equally, there may be two or more ways of aiming at a particular therapeutic result without either or any such approach demonstrating carelessness in any regard. As senior judges have more than once remarked, medicine is an inexact science. It is this "inexactitude" which gives reason and justification to alternative approaches to the same desired end.

It is this inexactitude, put in the most felicitous and complimentary way, which affords the practice of any branch of the medical art (or science) a protection in the field of legal practice more extensive than that enjoyed by any other profession. However, it must be said that the great majority of cases do not reach the level of litigation. Primarily because carelessness is often so obvious to everyone, including medical expert opinion, it is clear that it would be futile to try to argue a way out of it. Arguments may still rage over the extent and amount of compensation paid as a result of clear liability, but that is a different issue.

Errors of Judgement and Legal Blame

There was never more protective a judge, where matters of allegations against medical practitioners are concerned, than the former Master of the Rolls, Lord Denning. In the celebrated case of Whitehouse *v.* Jordan (1980), Lord Denning said: "We must say, and say firmly, that in a professional man an error of judgement is not negligence". For that he was sharply criticized when the case went on final appeal to the House of Lords. It was a case in which a woman whose child had been born with severe brain damage sued a then senior registrar obstetrician (later a consultant), alleging that he had pulled too hard and too long on Kiellands forceps and in so doing had caused the brain damage which was the subject of the complaint. The trial judge (High Court judge) awarded £100000 damages to include interest. The Court of Appeal reversed his decision, and in the course of doing so Lord Denning uttered the statement just quoted. Although the House of Lords for legal reasons agreed with the Court of Appeal, and therefore refused the mother and her child damages, it was made clear by their Lordships in the House of Lords that the expression "error of judgement" in the present context is wholly ambiguous. It may or may not be a careless or negligent error of judgement, according to circumstances and received medical opinion. To say, in answer to an allegation that such and such an action was negligent, that it was merely an "error of judgement" is merely to restate the original problem in a more obscure form, and not to solve it. It is not semantics, but rather the input of informed medical expert opinion and the ultimate determination of the court on that basis which will give an answer to the question, whether or not such and such a practice was negligent and therefore the proper basis of a compensation award to the victim.

A practice "rightly accepted as proper"

A most important rider must be added to what has just been explained. If the professionalization of any branch of medical practice is not to involve exclusivity of judgement of the legal as distinct from the professional consequences of a given action, the law must always reserve to itself the right to step in if it considers that a particular practice is unacceptable. The law has very rarely done this in the field of medical practice. Nevertheless, the law's prerogative to do this must exist if it is to retain ultimate control over the broadly stated regulatory parameters within which professional judgement can hold sway. It is for this reason that the then Lord Justice Donaldson (now Lord Denning's successor as Master of the Rolls) said, in the case of Sidaway *v.* Bethlem Royal Hospital and the Maudsley Hospital Health Authority, when the case was in the Court of Appeal in 1983, that it is necessary not only to look at what is accepted within any particular profession, but more particularly at what is "rightly" considered as acceptable and proper by that profession by an established body of opinion within it.

It so happens that the Sidaway case involved a question of negligence, but a question of negligence of a very different order from those which have been under discussion so far. In particular, no allegation whatever was involved of carelessness in the neurosurgical operation which caused the paralysis of which Mrs Sidaway complained to the courts. It was a case which involved the different and vexed question of "informed consent".

Informed Consent and the Disclosure of Risks

Every anaesthetist will be familiar with the common practice of getting consent from a patient who is in prospect of submitting to an anaesthetic procedure. The signature follows, or should in proper practice follow, an adequate explanation in broad terms of what is intended to be done. In the normal case of further surgical procedures following anaesthesia, both explanation and signature as evidence of consent will, respectively, be broad enough to refer to the surgical aspects of treatment also. Desirable as it is, the practice of getting the patient to acknowledge consent by signature of a form is legally rather odd. Odd, not in the sense of its being done in the context of proposed anaesthetic, surgical and exploratory procedures, but in the sense of its not being done in most if not all other cases of medical treatment.

A signed consent form is not a consent in itself but merely evidence of a consent. The substance of the matter is that the patient has, on the basis of an explanation in broad terms of what is proposed, consented to the prospect of that being done. The existence of a consent form is just that—a form. It is evidence, but only evidence, of the fact or substance of a past consent. Provided that past consent is not withdrawn, it can be assumed to be a continuing consent, and treatment may lawfully be given upon its basis. Any withdrawal or variation of the original consent will, however, have the definite legal effect that treatment may not proceed precisely on the original basis envisaged, despite the fact of a consent form having been signed at some time past.

It is the law of trespass which governs the rudiments of medical practice in this regard. The law of trespass depends essentially upon whether physical contact is or is not involved in what is proposed. An unconsented to and unwarranted physical contact amounts to a trespass, in the form of a battery. A battery involves unconsented and unwarranted physical contact. Assault involves the apprehension of the immediate infliction of such contact. Assault and battery may, for civil law purposes, be both involved in one and the same series of action. Even if some physical contact has been consented to, further procedures or treatment involving physical contact may still in certain circumstances constitute a battery. Subject to the certainly existing, although vaguely defined, bounds of the justification or defence of necessity at common law, it is an actionable battery to go beyond treatment A and on to treatment B when it is only treatment A to which the patient has consented. Sterilization, carried out without the prior consent of the patient, immediately following an abortion and performed under the same anaesthetic, may constitute a typical example.

To avoid an action in trespass, or more specifically battery in the present instance, what is required of the practitioner or person acting on his or her behalf is a "broad terms" explanation to the patient in order to get such consent as will form a complete defence to an allegation of battery at common law. It follows as a corollary that the level of understanding in the patient may itself be only fairly rough and "broad" if such legal justification for what otherwise would be a battery is to be established.

The matter of "informed consent" is totally different. "Informed consent" is not in itself a term which has any particular impact. However, it happens to be a term which is extremely useful to distinguish the type of situation just discussed, in which a broad consent is required to avoid what would otherwise be a battery, from a situation in which there is no question but that such a broad consent has been obtained, yet nevertheless the patient complains that he or she did not receive an adequate explanation of risks inherent in even the most carefully performed procedure. Known risks in normally successful and troublefree procedures are typical examples. In Mrs Sidaway's case, the known risk was neurological in nature and was assessed in proportional terms as being a 1–2% risk. She underwent a delicate neurosurgical operation in which the risk of a sequela was of that magnitude. It was Mrs Sidaway's tragic misfortune to suffer a major sequela. It was in respect of that consequence that she sued her doctor, a distinguished neurosurgeon. So slowly grind the wheels of the legal process, however, that her case eventually reached the House of Lords in December 1984, the neurosurgeon having himself died in 1977. Mrs Sidaway eventually lost her case, and a very substantial (if not decisive) factor in her inability to establish her entitlement to damages compensation was the lack of cogent evidence which existed by that late stage.

Informed Consent in Practice

It is not possible within the confines of this article to examine the function of a legal duty to volunteer information as to risks. It is the consequences of the fulfilment of that duty which are commonly referred to under the umbrella-term "informed consent" on the part of the patient.

However, medical practitioners who may fear that a standard of disclosure higher and more detailed than the mere "broad terms" explanation (which will suffice as a justification for what would otherwise be battery) would involve reciting the most complex clinical detail are fortunately mistaken in their fear. Specifically, the disclosure duty in relation to inherent risks is not simply, indeed at all, a duty to explain "more of the same" and in greater detail. It is, rather, a duty to go some way to canvass the social, financial, domestic, emotional and associated consequences which would be entailed in the materialization of a small but known risk in the case of the particular patient involved. It is duty not to recite merely clinical detail, but to treat the patient against a much broader background. In this instance, the law is attempting to set the context, social, financial, domestic and so forth, in which the acceptable and proper relationship between treater and treated is to be pursued. It is yet again a legal duty set in the most general of terms, within which particular approaches to its fulfilment may vary enormously according to the nature and incidence of the treatment and the particular people involved. Nonetheless, as is the case with all legal duties, it is a responsibility which needs to be understood if professional responsibility and clinical judgment are to proceed in an informed and unfearing manner.

EDITOR'S NOTE: John Finch is Editor of the *Personal and Medical Injuries Law Letter* published 10 times a year by Legal Studies and Services Ltd, Bath House (3rd Floor), 56 Holborn Viaduct, London EC1A 2EX.

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PITFALLS IN ANAESTHETIC PRACTICE

J. E. UTTING

There can be little doubt that more and more patients now instigate legal action against members of the medical profession in an attempt to gain damages. It is largely a fruitless exercise to contemplate why this should be so. Doubtless many factors are involved: the level of knowledge of medical matters in the population has increased from television programmes and the like; society has less respect for authority and patients are no longer in awe of the doctor; expectations with regard to health and longevity have increased; perhaps society has become more money-conscious, and so on. In addition, sums awarded in damages, or agreed out of court, have greatly increased. It is true that they have not, in the U.K., reached the vast amounts awarded in the U.S.A., but the acceleration in this country has been both remarkable and alarming.

In all this the anaesthetist is peculiarly, although not uniquely, exposed. Anaesthesia is safe and the expectation, therefore, is that the patient will always recover completely and never be damaged by it or during it; and so, the argument runs, if anything happens it almost certainly must be the anaesthetist's fault.

For an anaesthetist, as for any other medical practitioner, avoiding litigation, or at least being successful in rebutting charges of negligence, depends on a number of disparate elements. Basically these are care, communication and annotation, although this presupposes knowledge, experience, and skill.

As with many other human activities, such as climbing a mountain or driving a car, it is useful to know what pitfalls others have fallen into and to profit from their experience; Wylie (1975), for example, published such an account under the evocative title "There, but for the grace of God....". For this reason, a survey of some of the situations in which anaesthetists have found themselves (or thought themselves) to be in legal jeopardy is of some value. In addition to a brief account of such situations, some of the precautions anaesthetists should consider will be outlined.

Defensive medicine

It could be asked to what extent anaesthetists, and medical practitioners in general, should be thinking about the risks of litigation whilst about their every-day duties. The answer should be, very little; their main pre-occupation is already with patient safety and comfort and, if this be central to the way the practitioner behaves, little more is required. Despite this it would have to be conceded that there are always some features of practice which are more of medico-legal importance than of direct patient benefit. An obvious example is anaesthetic note-taking, which is often of little or no value to the patient, but may be of crucial importance in defence against litigation.

Practice which is governed primarily by the doctor's desire to avoid litigation and damages (to "cover himself") rather than a desire to act in the patient's best interest, which becomes subsidiary, is usually described as defensive medicine. An obvious example is given by the practice of x-raying, after injury, bones which can have only the minutest chance of having been fractured (Hawkins, 1985). In anaesthesia a parallel might be the ordering of preoperative investigations on patients who are young and healthy, despite the fact that the chances of finding anything which would influence treatment are remote; ordering an ECG on a symptomless and apparently healthy woman of 20 years would be an example. When confronting this sort of problem, and many others, the rule is to be guided by what one thinks one's colleagues would consider to be good medical practice. For this reason one would not need, even before major surgery, to order a chest x-ray on a symptomless, non-smoking man of 30, but one would on a man of 70 yr. There is not complete agreement on the subject (see Roizen (1981) for a fairly full discussion on the subject); there cannot

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be hard and fast rules about every investigation required. Judgement of an individual nature is required; thus special investigations may be indicated by features of the patient's history or by the results of clinical examination.

It is little use ordering preoperative tests to assess the patient if the results are either unavailable before surgery or are available but are not consulted. It is uncommon to find, on the routine preoperative chest x-ray, an important abnormality which influences treatment; but the author is aware, in his own practice or that of his immediate colleagues, of several cases in which such abnormalities as pulmonary tuberculosis and carcinoma of the lung have been missed because the x-ray was not inspected before the patient was operated on. If a preoperative test is deemed necessary it would be unwise not to have found out the results before anaesthesia is induced.

It could be argued that, if the result of a preoperative test was not available, an elective operation should be postponed. This may often be true: for example, to anaesthetize a patient with labile diabetes when no blood sugar analysis is available is fool-hardy and wrong. However, the patient whose operation is postponed has suffered an unpleasant experience, and this should be avoided if possible. There are circumstances in which it would be proper to proceed without the results of a test which has been ordered. For example, it would be wise to ask for an estimation of the haemoglobin on a woman of 40 yr with a femoral hernia. If the result were not available before surgery, it would not be unreasonable to proceed (in the absence of signs of gross anaemia), especially if it had been necessary for her to make elaborate arrangements for someone to look after her children.

An example of defensive medicine, and of the baleful results which may accrue from it, is given by the present position of halothane with regard to hepatic damage. It is probably true that halothane does cause hepatic dysfunction, albeit rarely, and that this phenomenon occurs more frequently when administrations of halothane are close together in time. The "rule" has gradually evolved that halothane should not be administered twice within 28 days, and it is now suggested that this period is too short and should be increased; and yet: "On the grounds of toxicity such a shift in practice is without real foundation" (Spence, 1986). Anaesthetists will find themselves impelled towards following new rules of this sort, although in so doing they will be using alternative agents which have not been proved to be safer and which cost more.

Other anaesthetists' experience

Accidents, it will be appreciated, are not usually simple events. Their causation is often complex and many factors are involved. For example, I might give adrenaline instead of atropine with fatal results. The reasons why I did this may not be immediately obvious. I might be tired (having been up all night), but yet feel unable to seek help (if, for example, I were a member of the junior staff, I might be thought lazy). I might be distracted or pre-occupied (perhaps having had an argument with my wife before leaving the house). Neither of these factors may be enough. The operating department assistant may, again for whatever reason, have put ampoules of adrenaline in the wrong box. Yet the accident would be classified merely as "drug error".

From this the lesson is not merely to avoid fatigue (although this may be important) nor yet to make sure that one does not have marital disharmony (although a pre-occupied anaesthetist is unlikely to act efficiently). The salient lesson is that all anaesthetists must realize that they are capable of giving the wrong drug in the operating theatre. If they are tired and distracted the possibility increases.

There are many mortality studies and some, although fewer, morbidity studies relating to anaesthesia and these are surveyed elsewhere in this issue. Among them are a group concerned with claims of possible, or actual, malpraxis (Utting, Gray and Shelley, 1979; Green and Taylor, 1984; Solazzi and Ward, 1984).

The study of Utting, Gray and Shelley (1979) gave an account of the anaesthetic incidents reported to the Medical Defence Union of the United Kingdom (M.D.U.) by some 2000 anaesthetic members during the 8 years 1970–77. More recently two of the authors, Gray and Shelley, have brought the account up to the year 1982 and the current writer is grateful to them for permission to use these data, which are marginally rearranged from those presented previously by Gray and Sperling (1985) to the Medico–legal Society of New South Wales. The total record is thus of 13 years. The rate of reporting has increased over the period. Thus from 1970 to 1977 inclusive the average was 75 cases reported per year; for the years 1978–82 inclusive it was 180,—an increase of two and a half times.

The study is of little or no epidemiological value. For example, the total number of anaesthetics to which the figures relate is not known. All it does is to give an account of situations in which anaesthetists thought themselves to be in danger of legal action because something unpleasant or disastrous had happened to patients in their charge. The numbers of each of the accidents are important only because they give a rough guide as to what are common and what are less common potential causes of litigation.

In some of the groups described the incidence of reporting must have been small. For example, probably only a small proportion of so-called anaesthetic deaths was notified to the Union; if the doctor, coroner and relatives were convinced that the death was unavoidable, it might well not be reported. Similarly, injury to teeth was probably only reported on a small minority of occasions. In some groups, however, reporting was probably much more complete; few anaesthetists, for example, would fail to report an accident which resulted in severe cerebral damage.

Another limitation of the study should be mentioned, although it is almost self-evident. The judgement of what the cause of individual accidents was is made by peer review by the Council of the Union. This is both informed and experienced, but it is not infallible.

TABLE I. *Summary of the 1501 untoward events reported to the Medical Defence Union between 1970 and 1982. (From unpublished data of Gray and Shelley, with permission)*

Deaths		591
Damage to teeth		387
Neurological damage		
Cerebral	159	
Spinal cord	27	
Peripheral nerves	64	250
Extradural foreign bodies (needles and catheter tips)		56
Superficial thrombophlebitis and minor injuries (abrasions etc.)		54
Awareness		55
Pneumothoraces		20
Extravasation of injected drugs		18
Lacerations, falls from table		15
Impaired renal function (mismatched blood)		9
Burns		7
Others		39
Total		1501

The analysis of the 1501 incidents reported to the M.D.U. between 1970 and 1982 (inclusive) is summarized in table I. In any analysis, cases of death and cerebral damage are of pre-eminent importance and these are dealt with first.

DEATH AND CEREBRAL DAMAGE

Most laymen would regard death associated with anaesthesia as the most serious of all anaesthetic accidents, representing the supreme failure to achieve what the anaesthetist set out to do. However, in some ways the infliction of severe cerebral damage can be worse. It is, of course, excluded from surveys of mortality and there is little on the subject in the surveys of morbidity.

Cerebral damage during anaesthesia can leave a residuum varying from slight mental or physical impairment to, unfortunately more usually, a state in which the patient is unable to care for him or herself in even the most elementary way, being spastic, unable to recognize or communicate with relatives and mentally crippled. The law, recognizing that the victim must be kept for the rest of his days and that this requires expensive facilities, awards very high damages in these circumstances. Lord Scarman referred to the problem in these terms: "It is cold comfort for the doctor to be told that his skills and the life support system which medical technology now places at his disposal are potent factors increasing the amount of awards. But this is the truth. It may be cheaper to kill than disable: and it may be more merciful" (Scarman, 1981).

It is almost invariably true that severe cerebral damage associated with anaesthesia is the product of incomplete resuscitation after cardiac arrest, often preceded by a prolonged period of hypoxaemia. The causes of death and of cerebral damage are, not surprisingly, closely similar; so similar, indeed, that they can conveniently be dealt with together.

An analysis of the 750 cases of death and cerebral damage reported to the M.D.U. during the years 1970–1982 is given in table II. Here an attempt has been made to classify the cases into those resulting mainly from misadventure and therefore defensible (37%), and those resulting mainly from error (63%) and therefore indefensible.

Little comment is needed on the group described as "Mainly misadventure". Numerically, the most important cause of death or

TABLE II. *Cause of 750 cases of death and cerebral damage reported to the Medical Defence Union between 1970 and 1982 divided into those thought to be mainly the result of misadventure and those mainly the result of error. Some cases of death or damage from hypotension and blood loss* might now be considered the result of error, as might some of the cases of halothane hepatic failure**. (From unpublished data by Gray and Shelley, with permission)*

Mainly misadventure	No.	%	Mainly error	No.	%
Co-existing disease	107	14	Faulty technique	326	43
Unknown	46	6	Failure of postoperative care	71	9
Drug sensitivity	39	5	Drug overdosage	34	5
Hypotension/blood loss*	32	4	Inadequate preoperative assessment	22	3
Halothane hepatic failure**	24	3			
Hyperpyrexia	18	2	Drug error	9	1
Embolism	14	2	Anaesthetist's failure	7	1
Clot in bypass	1				
Total	281	37	Total	469	62

cerebral damage was co-existing disease and the co-existing diseases which led to death or cerebral damage were usually cardiac or ventilatory. The patient was very ill before anaesthesia, was usually known to be ill, and did not survive, but the anaesthetist did everything which could reasonably be expected of him.

It is worth commenting on the cases in which the cause of death or cerebral damage could not be ascertained; those who investigated the cases were not sure what had happened. Such instances tended to be more common in the earlier years of the series and to be especially associated with anaesthesia in the dental chair.

It does not necessarily follow that, because an accident is described as "Mainly misadventure" there could be no medico-legal consequences. This is well illustrated by the group of catastrophes being described as the result of drug sensitivity. The anaesthetist would have to take note of any history of drug sensitivity and allergy and, anyway, if a reaction occurs he would be expected to treat it as best he can. If a patient were to die of blood loss, the anaesthetist would have to show that he took reasonable steps to keep the patient alive; and he would not, of course, be considered blameless were he to ignore a family history of malignant hyperpyrexia. Doctors who are not anaesthetists cannot fully evaluate anaesthetic mishaps: if, for example, a house surgeon elicits such a history of mishap in the family, it is up to the anaesthetist fully to evaluate the situation and to determine its importance.

It is also worth commenting on the fact that what was defensible yesterday may become indefensible today. An obvious example is given by the group described as "halothane hepatic failure": in the present climate anaesthetists would be held to be in error if they gave a second halothane anaesthetic too soon after a first or, in any case, if it were known that there had been a previous reaction (jaundice, pyrexia) to halothane at any time in the past.

Mainly Error

The group of major catastrophes which were considered to be mainly caused by error are the more interesting and instructive. Each requires separate mention. Some comments on avoiding the accidents are included in a later section.

Faulty technique

The pre-eminent cause of error was faulty technique; details are given in table III.

Errors associated with *tracheal intubation* are the most important group. Misplacement of the tube, that is oesophageal intubation which was not recognized at the time, was the most common accident; with the exception of viewing the tube in front of the arytenoid cartilages, there are no absolutely infallible indications that the tracheal tube is in the right place. This subject is dealt with later. Less commonly, death or cerebral damage was caused by prolonged, and often unnecessary, attempts at intubation which led to hypoxaemia; sometimes kinking occurred after the tube had been passed. Finally, there is a group of cases in which the actual technique of tracheal intubation was inappropriate for the circumstances; for example, the use of thiopentone and suxamethonium may be inappropriate in patients with

TABLE III. *Causes of the 326 cases of death and cerebral damage reported to the Medical Defence Union between 1970 and 1982 and thought to be the result of errors in technique. (From unpublished data by Gray and Shelley, with permission)*

	No.	%
Errors associated with tracheal intubation	100	31
Misuse of apparatus	75	23
Inhalation of gastric content	47	14
Errors associated with induced hypotension	26	8
Hypoxia	14	4
Obstructed airway	14	4
Accidental pneumothorax/ haemopericardium	13	4
Errors associated with extradural analgesia	9	3
Use of N_2O instead of O_2	7	2
Use of CO_2 instead of O_2	6	2
Errors associated with Bier's block	5	2
Underventilation during anaesthesia	4	1
Use of halothane with adrenaline	4	1
Mismatched blood transfusion	1	
Vaso–vagal attack	1	
Total	326	

upper respiratory tract obstruction—as in Ludwig's angina.

Misuse of apparatus was also a peculiarly common cause of death or cerebral damage. Of these, accidents involving pulmonary ventilators were the most common. They were not usually of a sophisticated type: usually the patient became disconnected from the ventilator, or the ventilator from the supply of fresh gas. Sometimes there had been misguided reliance on ventilator alarms, which can easily be turned off, and on air entrainment devices.

In a number of cases misconnection of gas circuits had taken place, resulting in the exhibition to the patient of nitrous oxide or of carbon dioxide instead of oxygen. In more than one accident the supply of nitrous oxide and of oxygen had been transposed either at the anaesthetic machine or between central supply and machine.

Inhalation of gastric content is still a fairly common accident, though not as common as it used to be. It is arguable that it may not be entirely avoidable, but frequently elementary precautions are omitted; for example, the suction apparatus may not be working correctly.

Induced hypotension in skilled hands is a safe and valuable technique (Enderby, 1980). Unfortunately, it is sometimes used for unnecessary indications in inappropriate operations and sometimes without the most elementary of precautions. To induce hypotension without a sphygmomanometer or other method of determining arterial pressure is totally indefensible, but unfortunately it has happened more than once.

Hypoxia is really a misnomer since most of the deaths resulting from error were from hypoxia in one way or another. Here, the term indicates accidents caused by failure of the oxygen supply, although this is less common as a cause of death and cerebral damage than it was before the days of "piped" gases. At the end of anaesthesia the patient is frequently allowed to breathe pure oxygen: unfortunately, there have been a number of cases in which either *nitrous oxide* or *carbon dioxide* have been used instead.

Failure to notice or to deal with an *obstructed airway* is usually the result of the anaesthetist's not being in immediate proximity to the patient. Death or cerebral damage as a result of *underventilation during anaesthesia* is less common and is usually attributable to inappropriate use of central depressant drugs or neuromuscular blocking drugs in patients who are breathing spontaneously.

Accidental pneumothorax may be caused by using apparatus incorrectly; accidental misconnection of the circle circuits is an example—the blow off valve may not be an adequate protection. Insertion of subclavian lines can also result in this complication, as can the use of the supraclavicular route for brachial plexus block. These latter accidents may not be entirely avoidable, but they should not cause a major catastrophe if the anaesthetist has the possibility in the forefront of his mind.

The reporting of accidents involving *extradural analgesia* has become more common in the past few years—doubtless because the technique is more widely used. Failure to minimize hypotension by administering i.v. fluids before the block was instituted; failure to treat established hypotension, especially in the frail and elderly; the use of too great a dose of analgesic; and intrathecal injection of the local anaesthetic have all caused major catastrophes.

Another important group of accidents with local techniques has been associated with the use of *Biers' block*. Leaking cuffs and releasing the cuff too early have both been responsible; specifically, the use of bupivacaine with this block should be avoided.

Failure of postoperative care

A considerable number of deaths and cases of cerebral damage still occur in the immediate postoperative period. Of these the major cause is ventilatory obstruction. All too frequently, the anaesthetist has left the patient in someone else's care before full recovery.

Drug overdosage/drug error

Some of the accidents reported have been deemed to be caused by overdosage of drugs or giving the wrong drug. Of the drugs involved in the former, thiopentone figures prominently among the induction agents and halothane among the volatile agents. Some room for doubt may well exist, but the administration of, for example, thiopentone 500 mg to a 30-kg woman, aged 86 yr in congestive cardiac failure is a clear cut example of overdosage. Exceeding the maximum permitted dose of local agents is also not uncommon; these are toxic agents, but the attitude towards them can sometimes be somewhat cavalier. Examples of errors in drug administration have been the use of potassium chloride instead of saline, and of halothane instead of methohexitone i.v.

Inadequate preoperative assessment

Preoperative assessment was deemed to have failed when patients were anaesthetized with undetected sickle-cell anaemia, with undetected bilateral pneumothoraces, with undetected hyperkalaemia and with dehydration and blood loss the severity of which had not been properly assessed. All of these were causative of death or cerebral damage.

Anaesthetist's failure

Here the anaesthetist was unable to do his job because he was, for example, under the influence of alcohol or drugs or mentally ill. In a number of other cases he had left the operating theatre.

OTHER ACCIDENTS

It is, of course, not only through the major catastrophes that the anaesthetist may be in medico–legal jeopardy. There are a number of other situations in which this can occur (table I).

Damage to teeth

Damage to teeth, although a frequent accident, is relatively trivial. However, it must be admitted that the anaesthetist can do grave damage to elaborate bridge work in a second or so and it can be expensive to repair the damage.

The spinal cord

The anaesthetist can damage the spinal cord either by spinal analgesia or, rarely, by the accidental dural tap associated with extradural analgesia. In the United Kingdom perhaps the most celebrated medico–legal case associated with anaesthesia concerned the production of chronic adhesive arachnoiditis in two patients who were given spinal analgesia (Roe and Woolley *v.* Ministry of Health, 1954). Judgement was given for the defendant anaesthetist on the grounds that the likely cause of the accident was the entry of phenol through minute and invisible cracks in the ampoules of local analgesic.

Despite the fact that judgement was made for the defendant, these cases cast a cloud over spinal analgesia in the United Kingdom and it is only recently that this technique appears to have emerged. Spinal analgesia can, in common with other techniques in anaesthesia, be safe if the technique is used meticulously. It is worth mentioning that the use of the wrong solution for spinal analgesia can be a massive disaster.

Injury to peripheral nerves

An injury to a peripheral nerve during anaesthesia still appears to be a common event and is almost always indefensible. Of the nerves injured, the ulnar (in the region of the elbow) remains the commonest. The facial nerves, the lateral popliteal nerve and the brachial plexus are also at risk if positioning of the patient is not correct.

It is unusual for the anaesthetist to give i.m. injections. However, anaesthetists have injured a number of nerves by not obeying the elementary instruction to use the lateral side of the thigh for this purpose. The opportunistic injection of cyclizine into the lower arm, for example, has resulted in paralysis of the anterior interosseous nerve.

Extradural foreign bodies

In the United Kingdom the use of extradural analgesia has burgeoned in the last decade. This has probably been largely a result of its increased use in obstetrics, although its use in anaesthetic practice elsewhere has probably increased as well.

It is not surprising that the number of accidents involving extradural analgesia has increased and that this increase is associated with a corresponding increase in litigation. The accidents involved have been associated with hypotension, total spinal analgesia, and the retention of fragments of catheter.

Superficial thrombosis and thrombophlebitis

Superficial thrombosis and thrombophlebitis are often held, quite unfairly, to be the anaesthetist's fault; judgement has been entered for the defendant on a number of cases in which, for example, the use of thiopentone has, very surprisingly, been followed by thrombosis. Fortunately, most patients are reluctant to do anything about what is usually a fairly trivial injury.

Awareness

There is little indication that the incidence of complaint over the problem of patients remembering something when they were thought to be completely unconscious under general anaesthesia has declined in recent years. This is despite the use of deeper anaesthesia than used to be the case. There are two factors to take into account: first, the drugs now used are not all necessarily efficient at obtunding consciousness. For example, fentanyl may reduce the incidence of awareness under anaesthesia, but the relationship between consciousness and the use of an analgesic agent as an adjuvant is obviously a complex one. The second point is that, although the depth of anaesthesia may be considerable during most of the anaesthetic, this may be of little consolation to a patient who has had a tracheal tube passed when wide awake early on in the procedure.

Pneumothoraces

The problem of the accidental pneumothorax has already been mentioned as a cause of death or cerebral damage. Often it is detected and no permanent harm comes to the patient, but it is unfortunate if a patient anaesthetized for, say, an appendicectomy becomes aware of a drainage tube in the chest shortly after recovering consciousness.

Extravasation of injected drugs

From time to time, every anaesthetist extravasates drugs which he is injecting. However, the injection of a large volume of solution can have unfortunate results, as can the injection of, say, thiopentone, to a nerve such as the median.

Lacerations and falls from the operating table, etc.

The anaesthetist obviously assumes direct responsibility for making sure that the patient is not physically injured whilst unconscious. It is properly the hospital authorities' responsibility to ensure that there is assistance to move the unconscious patient. It is, however, generally the anaesthetist's responsibility to oversee the procedure when the patient is unconscious, unless this responsibility has been handed on to someone capable of receiving it. Letting the patient fall is usually an inexcusable breach of that responsibility.

Impaired renal function—mismatched blood

The commonest cause of a transfusion reaction is clerical error. The source of this is likely to be in the haematology laboratory, but it can be in the operating theatre. Surprisingly, the patient's name can be the weak link and a slip provided for another patient may be accepted. Errors can, of course, result in death or in permanent or temporary renal damage.

Burns

There is still a small number of patients who receive burns during surgery. Most of these are from diathermy, although some arise from the use of the diathermy in the presence of inflammable skin preparations such as ether.

A miscellany

Corneal abrasions are not uncommon: the obvious cause is the contact of the open eye with drapes during surgery in which the head must perforce be covered—for example, in thyroidectomy. However, such abrasions can also occur when the patient is being moved, especially onto the abdomen. A restless patient also can inflict an unpleasant corneal abrasion on himself by catching his eye with a finger nail.

There are a number of minor injuries which can occur when the patient is asleep which the anaesthetist must be at pains to avoid. Abrasions, particularly of the face, can be caused, particularly during movement; bruising and other injury can be caused to arms which have been left on a board as the patient is brought into theatre from the anaesthetic room.

MINIMIZING THE DANGERS

There is no way of being absolutely sure of avoiding litigation, or at least the threat of it. Some steps, however, can be taken to minimize the risks. Of these the most obvious are the most effective.

Preoperative Preparation

Ideally, every patient presented for anaesthesia, general or local, should be seen by the anaesthetist who will give the anaesthetic. This is, however, quite impracticable; indeed, it is not always possible for every patient to be seen by an anaesthetist. One is left with the rule that, in hospital practice, every patient should be seen by a doctor and the anaesthetist, except in dire emergency, must satisfy himself that the preoperative assessment has been competent.

In dental practice this is usually not possible. Even so, dental anaesthesia has a good safety record statistically, although every dental anaesthetic death, being totally unexpected, is especially tragic. In the dental surgery the salient rule for safe practice would seem to be to accept for anaesthesia only those who appear, on reasonable questioning, to be healthy. Many dental practices, and dental hospitals, have a check list of questions on health, symptoms and medication which are routinely asked before anaesthesia is administered. These are probably more satisfactory than mere casual questioning.

History

This should include the usual features of asking about the patient's symptoms, previous illnesses, current drug treatment, allergies, surgical operations and anaesthetics. In many cases this will have been done before the preoperative anaesthetic visit, usually in the ward, and the anaesthetist may merely seek what amplification he thinks necessary.

It would be difficult to justify an anaesthetist's giving an anaesthetic when he or she was *unaware* that the patient had had a recent myocardial infarction, was receiving antihypertensive drugs or insulin, or had a previous anaesthetic with halothane one week before. Yet these situations do arise from time to time.

Examination

Again, there may be no need for the anaesthetist to conduct a physical examination if it has already been performed. Sometimes, however, he will wish to check or further assess findings for himself. Sometimes, too, careless gaps may have to be filled—for example, the arterial pressure measured. Most anaesthetists with some experience will admit that, on occasion, they have recognized and detected clinical features which had previously been missed or not noted; for example, those of congestive cardiac failure. It is often useful to examine the patient, especially when a newly qualified house surgeon has done so already.

The dental state

A visit to the patient should include a brief inspection of the teeth. If dental care is so bad as to make it obvious that damage may well be done, the anaesthetist would be within his rights, in an elective case, in requiring the patient to seek advice from a dental surgeon before anaesthesia. In practice this happens but rarely, and sometimes one may be left with the strong possibility that damage may be done because, for example, a front tooth is very loose. The anaesthetist should explain this fact and that an extraction may have to be performed when the patient is anaesthetized if it is thought that the tooth could be dislodged by laryngoscope or airway. Again, the anaesthetist would be in his rights to explain that the patient must acknowledge that this advice has been given to him; this can sometimes be done on the consent form. However, it may be preferable for the anaesthetist to explain to the patient in front of witnesses and note this fact in the case sheet.

It goes without saying that the anaesthetist should insert the laryngoscope, and the airway, gently, and should not use the upper teeth as the fulcrum of a lever; the use of a guard on the teeth may be appropriate in some instances. If a tooth has been dislodged, it is encumbent on the anaesthetist to be able to account for it. An inhaled fragment must obviously be removed at bronchoscopy.

If the teeth have been damaged during anaesthesia, the anaesthetist should speak to the patient and obtain expert and immediate dental treatment for him if at all possible. This certainly reduces, but does not eliminate, the chance of subsequent action by the patient.

Investigations

The problem of investigations has been mentioned already when dealing with defensive medicine. Although most patients are probably subjected to more investigations than is necessary, it is essential to perform urinalysis on every patient. More specialized investigations, such as pulmonary function tests, may be indicated by the history or by the examination.

Blood

The ordering of blood before surgery is usually considered to be the duty of the surgical staff. The anaesthetist should check that the appropriate grouping and cross-matching has been ordered, and that it is immediately available before surgery in which considerable blood loss is expected.

Preoperative medication and treatment

Drugs ordered before operation and their dosage have to be prescribed legibly and, of course, the dose must be appropriate. The anaesthetist may feel, and may be, quite competent to construct the regimen for a patient with, for example, diabetes mellitus. However, especially if the case is not entirely simple, he would be wise to consult a physician; in these, as in other fields, the doctor must seek advice when the question no longer lies within his field of competence.

Consent

The consent form must be signed, but the patient signing the form is not signing a blank cheque. It is impossible to be dogmatic about what a patient should be told before anaesthesia; as a generalization, it might be said that more information is required now than used to be the case some time ago; the tendency is to give patients more information, not less. It is not generally regarded as necessary to inform patients of tragic and rare complications, such as the possibility of anaesthetic death; it can be helpful to mention the more common ones such as sore throat. In all events, the patient should be given the opportunity to ask questions.

Opinions differ about whether or not a patient should consent to extradural analgesia in midwifery; it is the writer's opinion that formal consent should be given. Certainly, if an extradural block is to be established after general anaesthesia has been induced, the fact should be discussed with the patient beforehand and consent for the procedure obtained.

The Anaesthetic

There are a number of accidents mentioned above for which the precautions are self-evident. This, for example, applies to checking drugs and blood. The patient's name and the side on which the operation is to be performed are also important; the anaesthetist would not escape blame if a mistake were made with either. In this respect it should be said that changing operating lists is an undesirable practice. Not to change them is a counsel of perfection; when they have been changed there is an additional hazard.

The machine and equipment

The checking of the anaesthetic machine and of the other equipment is an area of divided responsibility between the hospital and the anaesthetist. The machine must be checked, including if possible a check with an oxygen electrode, by someone competent to do so at the beginning of the day; the anaesthetist himself must see that the machine and the circuit are in working order, and that the circuit is connected correctly before each case. There are different ways in which checking can be done and which method is to be used should be decided as a matter of policy.

It is unnecessary for the anaesthetist to know every working detail of every piece of equipment he uses, for example, a pulmonary ventilator. He or she should, however, be familiar with the functional principles and know the common faults which may occur.

Induction

The elementary precautions of withdrawing blood, of watching the injection site and of asking the patient if the injection itself is painful are obviously important. To some extent thrombosis and thrombophlebitis in veins must be regarded as unavoidable, but it would now be difficult to justify giving diazepam into a small vein in the back of the hand other than in an oil-in-water suspension.

When dealing with a patient who is in danger of inhaling gastric content the anaesthetist would be expected, before induction, to check the suction apparatus, the laryngoscopes and the tracheal tubes. He must satisfy himself that the person who is to provide pre-cricoid pressure knows exactly how to do so and would, of course, be expected to pre-oxygenate the patient before induction.

Lunn and Mushin (1982) emphasized the need for skilled assistance for the anaesthetist and this is particularly so for a patient who may have a full stomach and to whom pre-cricoid pressure is to be applied. In obstetric anaesthesia, in which inhalation of acid gastric content remains a major source of mortality and morbidity, the anaesthetist must weigh the advantages of various prophylactic regimens.

Tracheal intubation

Checking the placement of a tracheal tube is of great importance,—the number of accidents which involve tracheal intubation is, as has been pointed out, a conspicuous feature of modern anaesthetic practice. There is only one way to be sure that the tube is in the trachea, and that is to visualize the artenoid cartilages and see that they are behind the tube; unfortunately this is not always possible and other methods, such as auscultation of the chest, are not infallible. Air entry to the lungs can be simulated when the tube is in the oesophagus and even movement of the chest can give equivocal results.

If there is difficulty with passing a tracheal tube, an inexperienced anaesthetist should, if possible, seek immediate help; he should not even attempt what is obviously going to be a difficult intubation without seeking help beforehand. A failed intubation regimen should have been thought out before such an incident occurs; continued and desperate attempts to intubate can kill the patient and this may happen despite the fact that it is easy to ventilate the lungs without passing a tube. Kinking and obstruction of the cuff may occur at any time, especially when the patient has been moved. All anaesthetists, senior and junior, should consider the aphorism "When in doubt take it out" and be aware that misplacement of, and obstruction to, the tube can mimic bronchospasm.

Positioning the patient

Although he does not perform the task himself, the anaesthetist must ensure that the patient is moved safely and correctly positioned for surgery. Thus it is the anaesthetist's responsibility to make sure that nerves such as the ulnar are not at risk when the operation begins, and that there is no possibility of the elbow slipping onto a hard edge, such as that of the operating table, during surgery. When necessary, other parts (e.g. the cornea) must be adequately protected. Undue pressure must be avoided, for example by metal connections on the face.

The anaesthetist should make sure that no part of the patient is in contact with metal and that the person connecting the diathermy is qualified to do so. Needle electrodes for the ECG can cause burns if there is a fault in the diathermy. Their use should be avoided.

If there be anything unusual about the position the patient has been put in, for any reason whatsoever, the anaesthetist should first make sure that there are no apparent dangers, for example, part of the body in contact with metal. Having done that it is as well to describe the position in the anaesthetic notes for future reference.

Pulmonary ventilators

Before using a pulmonary ventilator the anaesthetist should be familiar with its mode of action, but not necessarily with the details of its construction; he should satisfy himself that it is in working order by using simple checks. Any apparatus which has been recently serviced must be viewed with suspicion. The connections must be checked and a circuit available independent of the ventilator so that manual ventilation can be used if there be difficulty. Ventilator alarms are not infallible and are no substitute for close observation of the patient: they can easily be turned off, and sometimes they may fail to act.

Monitoring

The best monitor is the anaesthetist in close proximity to the patient. The only person to whom he can delegate this responsibility is another anaesthetist: neither a nurse nor an Operating Department Assistant will do. Not to remain with the patient continuously will almost certainly be considered negligent.

Monitors are for perceived needs in patient care and are not there merely to give an appearance of technological achievement. There is a medico–legal danger in making it appear negligent not to have a particular monitor in a particular situation: it would be unfortunate, for example, if it became accepted by the profession that it is wrong to anaesthetize a patient for, say, a removal of in-growing toe-nail, without having ECG, sphygmomanometer, capnometer, oxygen analyser and the like. Circumspection is required.

Emergency Procedures

These can cause great difficulty, especially in obstetric practice. First, there is the clinical problem of weighing the need for resuscitation against the need for early intervention. Second, facilities are often not as good in emergency theatres as in the main theatres, and out-of-hours staffing is often inferior. Third, junior staff are usually responsible for treatment. These may seem to be arguments for not bringing doctors to book for things which happened in the course of emergency treatment. Relatives of a plaintiff who has suffered in these circumstances, however, may well feel differently. They are right to do so: it is often true that facilities for emergency treatment are not as good as they should be.

Junior staff should expect advice, assistance and support from senior colleagues when they are dealing with emergencies, and junior staff should feel able freely to consult with seniors and to discuss the facilities available. It must be a good rule that senior staff themselves work in places in which emergency anaesthetics are given in order to appreciate what conditions may be.

Postoperative Care

The anaesthetist must accept the primary responsibilty for the patient until he or she is able to maintain an airway, void gastric content effectively, and is conscious. He must also make sure that the patient is breathing adequately and the cardiovascular system is as stable as it can be. He must either discharge this obligation himself or ensure as far as he possibly can that the person whom he has deputed to look after the patient is competent to do so. This would probably mean another doctor or a trained recovery nurse. If anything goes wrong at this stage, the anaesthetist may have to defend his decision to hand over the immediate care of the patient.

The Council of the Association of Anaesthetists of Great Britain and Ireland and the National Association of Theatre Nurses have published the results of a joint working party on this important topic (Eltringham, 1986). There is no doubt that strict observation of the procedures they support would result in the elimination of most of the accidents which occur in this period.

Some of the suggestions of the working party can be outlined. The patient should be sent to the recovery room under the supervision of the anaesthetist or recovery room nurse, on a tipping trolley or bed on his or her side. Adequate information must be provided in writing (e.g. name, operation, anaesthetic indication) and adequate instruction given (e.g. on fluids, medication, oxygen therapy, catheters and packs). The nurse must know where anaesthetic assistance is available. Trained nursing on a continuous, individual, one-to-one basis is required until the patient is able to maintain his or her airway; the nurse should have no other duties at that time. The patient should be kept in a suitable recovery room until the criteria for discharge are met. During this time observations must be made and recorded; a specifically designed chart may be required for this purpose. Nursing staff can administer drugs only if they are correctly prescribed; they should not administer drugs i.v. unless specially trained and unless it be the agreed policy of the hospital.

Before the patient is discharged from the recovery area, the staff must normally satisfy themselves that (s)he is conscious, reflexes have returned and the airway can be maintained. In addition, breathing must be adequate, a good colour must be being maintained, the cardiovascular system must be stable and adequate analgesia must have been provided.

The anaesthetist would no longer be considered responsible for the future treatment of a patient when he handed over the care to the staff of an I.T.U., providing it was clearly understood that the transfer of responsibility had taken place (You'll be looking after him now, won't you? I'll call and see how he's getting on) and that the transfer is in the patient's best interests. It would be hard for a consultant to justify handing over treatment to an I.T.U. staff if the most senior doctor was an S.H.O; in these circumstances he would be expected to keep an interest in his patient.

Miscellaneous

Awareness during anaesthesia

It is wise to use a low concentration of volatile adjuvant to nitrous oxide when a neuromuscular blocking drug is used. This, however, is no protection against slipshod technique: for example, the patient may remember tracheal intubation even if, thereafter, a relatively high concentration of volatile agent is used. It is quite clear that it is wrong to meet the patient's claim of awareness with a blank denial and a failure to communicate. The patient knows that something has gone wrong and feels that the medical staff are both covering up and treating him, or usually her, as a person of low intelligence. Talking sympathetically can be therapeutic.

It is a matter for debate as to whether patients at high risk, for example patients undergoing Caesarean section, should be told of the risk that they might be aware. This is obviously a matter for decision by the anaesthetist, judging the condition of the patient and fetus and the possible reactions of the patient. The fact that the patient has been warned does not, of course, automatically exonerate the anaesthetist should the patient subsequently be aware or have pain, or both; it does, however, demonstrate quite clearly that this important complication had been thought about.

Extradural analgesia

The main method of minimizing accidents from extradural analgesia is to use meticulous technique; in addition, however, the anaesthetist must make sure that the standard of nursing is good enough to deal with this exacting group of patients. If "top-ups" are to be given, the knowledge and skill of those giving them must be adequate and there must be adequate staffing and facilities.

If a small fragment of extradural catheter is left *in situ*, the accident must be carefully reported in the notes and the patient's general practitioner must be informed; telling the patient is a matter of medical judgement. It is unusual for a fragment to give rise to problems; if it does the opinion of a neurologist should be obtained.

Anaesthetic record

The anaesthetic record is primarily intended as a guide for those who may give subsequent anaesthetics; for instance, it will record any difficulty which has been encountered (for example in passing a tracheal tube) and give an indication of what drugs have been given so that, for example, halothane may be avoided for some time after an anaesthetic with this agent. It may, however, assume crucial medico-legal importance since it may have to be produced, with other notes, in a court of law. It is important, therefore, that it is not lost.

It is impossible to say dogmatically what an anaesthetic note should contain, but it should certainly include the agents and drugs used and their doses, an account of the fluids administered, the technique and circuit used, special protective measures (eyes covered during thyroidectomy) and the position of the patient (if unusual,—it is hardly necessary to observe that dilatation and curretage was performed in the lithotomy position). Recordings of the limits of heart rate and arterial pressure observed at frequent intervals show slow changes and can be clinically useful. Failure to record in this way can give a judge an unfortunate impression of waywardness. Legibility of anaesthetic records is, unfortunately, all too often poor, and there are often incomprehensible abbreviations.

Serious accidents should be recorded in the case sheet in full, with an account of drugs given; the date and time should be recorded. Some thought should go into a note of this sort. Once it is inserted it becomes a matter of record and may have to be produced in court. It is there as a clinical record, not as a thesis on the possible causes of an accident. Admissions of responsibility or the attribution of responsibility are to be avoided: "Patient exsanguinated because surgeon split aorta" is a gratuitously revealing comment, as is "Anaesthesia associated with gross hypoxia ?cause ?anaesthetic death"—but a Consultant Anaesthetist has been responsible for the former comment and a Consultant Surgeon for the latter.

The account of an accident must be adequately detailed for the anaesthetist to use it as an *aide-memoire* at a later date and as part of a letter to his Defence Society. Such a note as "T.250 mg--N_2O/O_2/hal.--cardiac arrest---resus.---ITU" is unlikely to impress a judge at a later date; indeed, it is so attenuated as to be insulting.

Notes should not be changed at a later date, nor should a note be removed from the case sheet and another account inserted, even if the other account is more accurate. On the other hand, it is legitimate to write a note later explaining an omission or making an amendment, providing the date is clearly shown.

Assistance for the anaesthetist

If the continuous presence of an anaesthetist during an anaesthetic is mandatory, as it is, then there must be adequate assistance. For the sophisticated equipment now in use, he requires extra help and he may need drugs and equipment which are present outside the theatre. At the induction of anaesthesia skilled help will be necessary with, for example, the provision of pre-cricoid pressure; again, at this time, skilled assistance may make all the difference between success and failure in the case of a tracheal intubation which turns out to be difficult.

In these circumstances the emergence of the Operating Department Assistant (O.D.A.) as a trained, professional group has made a considerable difference and a trained O.D.A. now rightly takes his part in the operating department team. A trained anaesthetic nurse occupies, of course, the same position. Neither, however, should accept responsibilities which are not properly theirs.

As has been noted, Lunn and Mushin (1982) have emphasized that absence of skilled assistance for the anaesthetist may be a cause of anaesthetic mishaps. Unreasonable failure to provide such assistance, despite requests, might well put the responsibility for an accident, at least partly, on the Authority which has failed to provide it. The fact is that the provision of such assistance on a comprehensive scale is expensive, but failure to provide it may be expensive, too, not only in terms of financial loss but in terms of human suffering as well. However, neither the trained O.D.A. nor the trained nurse is, in any sense, a substitute for a second anaesthetist in very difficult cases.

Talking to patients and their relatives

Defence societies, in common with car insurance companies, advise their members not to make direct admissions of liability. Usually there is nothing to be gained and much to be lost by an admission and a subsequent defence can be prejudiced or ruined by it. However, failure of communication with patients and their relatives arouses suspicion that something has gone wrong and that someone is to blame; and refusal to talk after a mishap can result in an understandable anger which seeks retribution. Failure to communicate, and prevarication, invite litigation.

The Defence Societies will always advise their members on what to say and on how to say it, and their advice should, of course, be followed. Two problems, however, remain: the first is what to say before they are consulted, the second is how to present what has to be said.

Relatives of patients who have died or suffered from unexpected, untoward injury are frequently upset, even to the point of irrationality. They are also impressionable, and what is said to them immediately after the event can set the seal on what will happen subsequently. It is also true that the doctor, who may know that he has committed an error, will also be upset and certainly unlikely to be at his best and most composed. He is vulnerable and may make damaging admissions. And yet it may be impossible or at least inappropriate to postpone an interview.

In these circumstances members of the junior staff can and should talk over the problems with a consultant, and it may seem best for the consultant to be present and take part in the interview. In any event the interview must be conducted with tact, with sympathy (a nervous doctor can easily appear callous) and, if appropriate with a promise to see the patient later on, the next day for example. In a fatal case the fact that the patient's death is being reported to H.M. Coroner (or the Procurator Fiscal) should be reported to the relatives and an explanation for this action given ("we always report deaths occurring within 24 hours of surgery and anaesthesia to the Coroner").

Patients or, in some circumstances, their relatives have a right, in natural justice, to know what has happened to themselves or their close relations. They should, subject to the limitations imposed by the Defence Society, be told all that is possible. To do this takes skill and maturity. Even if litigation does not result from an accident, a relative convinced that the doctor has been negligent and does not care is a sign of failure of the profession.

Just as lack of honesty can invite suspicion, so can a patronizing attitude do great harm. For a doctor to say to a patient who has lost two front teeth during a Caesarean section "Don't be a silly girl. You're still quite pretty" is to invite legal action, especially when the "girl" is a solicitor of 37.

Reporting accidents to the defence organizations

Any untoward event which has been seen to occur to the patient whilst under the care of the anaesthetist or whilst under the care of someone whom the anaesthetist has delegated to look after the patient should be noted to the Defence Society first, perhaps, by telephone and then in a letter. If there is doubt as to whether to report fully or if urgent advice be required, then a telephone call to the appropriate organization is clearly in order.

Complaints by patients should always be taken seriously and the complaint reported to the defence organization. However, it is unnecessary to report every death associated with anaesthesia if it is quite certain that the disease process of the patient was the cause and not anaesthesia or surgery.

It is unfortunately true that the patient's suspicions of his treatment can be aroused by other doctors who say tactless things. There were few plaudits for a surgeon who said to a relative of a woman who had a degree of brain damage "I think the anaesthetist let the breathing circuit fall to bits"—especially as this was not true.

Organization

The primary purpose of such structures as Divisions of Anaesthesia is to improve patient care, and this includes comfort and safety. They play a vital role in making sure, as far as is possible, that the anaesthetic staff work in the most efficient way and that sick patients are anaesthetized by staff who are adequately competent and experienced. The organizational side of this work is sometimes neglected.

This duty may in part be discharged by morbidity and mortality meetings, by using critical incident analysis, and by setting standards of safe practice. In this last respect there is a duty to ensure that facilities are adequate and that equipment is maintained to satisfactory standards. If this is not so, deficiencies must be brought to the notice of employing authorities, using the channels which are available for this purpose.

CONCLUSIONS

A knowledge of accidents and mishaps is useful to the clinical anaesthetist: it must, indeed, form part of the basis of training. However, practice is not merely the avoidance of pitfalls; to look at it in this way is to be negative to an extreme degree. It is the rules for avoiding pitfalls which are important, not so much the pitfalls themselves. One of the arts of teaching and training would seem to be of using accidents as hat-pegs for instruction, without inducing a neurotic attitude to the specialty.

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ANAESTHESIA AND THE LAW: THE NORTH AMERICAN EXPERIENCE

F. W. CHENEY

In the United States, professional liability has become of increasing concern to the medical profession in general and to the anaesthetist in particular. Anaesthetists, in addition to practitioners of other high-risk specialties, have experienced dramatic increases in their professional liability insurance rates, and increasing numbers have become targets of professional liability claims.

Professional liability suits were rare until the 1930s. After World War II, a steady increase began in professional liability claims against health care providers, a trend which continued through the 1960s (Walt and Golin, 1984a). In the mid-1960s the Federal Government assumed much of the financial responsibility for the care of all citizens older than 65 years eligible for social security (Medicare) and also for citizens with incomes below certain levels (Medicaid). The increased government involvement and the impact of liability insurance on the cost of care led to the appointment in 1971 of a Presidential Commission on Medical Malpractice. The Commission cited several reasons for the increase in malpractice activity. More people were getting medical care, and the care itself was becoming more complex. While new diagnostic and therapeutic procedures saved lives, they also increased the number of adverse results. The growing magnitude of the problem at that time is illustrated by the statistic that 80% of all malpractice claims filed between 1935 and 1975 were filed during the last 5 years of that period (Walt and Golin, 1984a). This increase in the number of claims between 1970 and 1975 had its impact on the insurance industry, and thus the "crisis of availability" of professional liability insurance in the mid-1970s came into being. Insurance companies increased their premiums significantly, or left the professional liability field entirely. Problems cited by the companies were large numbers of claims, increasingly liberal jury and court awards, inflation, and the long "tail" (see below) on malpractice claims. As only 10% of malpractice claims were filed in the year of their origin, insurance companies were unable to predict accurately their losses for setting rates. Most professional liability insurance at that time was in the form of occurrence policies which permanently covered the insured for all maloccurrences in a given year. Insurance companies were paying out on claims up to 10 years after the event and, as inflation was rampant, payments were far in excess of the premiums collected earlier (Walt and Golin, 1984a).

The response of the medical profession to this "crisis of availability" was to seek legislative relief at the state level. Laws were proposed in many states which would shorten the statute of limitations, put a ceiling on awards, limit plaintiffs' lawyers' contingency fees, and set up screening and arbitration panels. In some states joint underwriting associations were set up to provide liability insurance for health care providers where commercial coverage was not available. These early attempts at tort reform met with varied success in some states, some proving ineffective and others succumbing to constitutional objections. The California Tort Reform of 1975 took 10 years before successfully passing all legal challenges to its provisions.

On the insurance front, many commercial companies switched from occurrence policies to claims-made policies, which made it easier for them to make rapid rate adjustments in response to escalating losses. Claims-made insurance provides coverage only for claims reported while the policy is in force. The major problem with this type of coverage is that it provides no protection from claims reported after the policy has lapsed. Therefore, when a physician retires, becomes

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disabled, changes location, or buys occurrence coverage again, he or she has to purchase insurance to cover the residual claims which may occur. This so-called "tail" coverage can be quite expensive if the physician has been insured under a claims-made policy for a number of years. Another significant development in the mid-1970s was the formation in some states of physician-owned, non-profit professional liability insurance companies. By 1977, 15 physician-owned, insurance companies were in operation, and by 1985 there were approximately 30.

By 1978, these various actions seemed to be resolving this initial crisis. Also, the number of claims seemed to be decreasing, suggesting that the legislative efforts toward tort reform were successful. However, this trend was illusory. The National Association of Insurance Commissioners (NAIC), which had begun to focus on losses from medical liability, noted that the cost of settling an individual claim had increased dramatically. Between 1975 and 1978, the inflation-adjusted cost of settling a claim increased by 44%. Million-dollar awards became much more frequent; for example, in 1975 only five settlements or awards equalled or exceeded $1 million, while 3 years later there were 23 awards. In the NAIC study, anaesthesia-related claims represented only 3% of total physician claims, but accounted for 11% of the total dollars paid. These figures emphasized the high cost of anaesthesia claims (Brunner, 1984).

Predictions of dramatic increases in losses came true with a vengeance, as by 1983 professional liability losses had increased to almost $2 billion from the $817 million registered in the peak year (1975) of the first crisis. The impact of the great increase in losses as a result of professional liability led to the "crisis of affordability" of the 1980s. Medical liability premiums in general increased by 80% between 1975 and 1983 (Walt and Golin, 1984a). This dramatic increase in premiums was not spread evenly across the country, and has not affected all specialties. The high-risk specialties, of which anaesthesia is one, were the hardest hit. In 1986, the Committee on Professional Liability of the American Society of Anesthesiologists completed a survey of professional liability rates charged by a large private insurance company which offers coverage in 40 states. The average premium for a claims-made policy was $1 million coverage for one event and $3 million aggregate for the year was approximately $25000. This amount of coverage, considering the overall liability climate in the United States, would be considered minimal. There was a wide range of premiums, from a low $8428 yearly in Arkansas to a high $49980 in urban Illinois. Locations with yearly rates in excess of $40000 were in the urban areas of California, Florida, Illinois, Missouri and Connecticut. Curious geographical differences exist: for example, Arkansas and Tennessee, both contiguous to Missouri, have yearly rates only 18–25% of that of their more expensive neighbour. Iowa and Nebraska are contiguous to each other in the midwest, but Nebraska's rates are approximately 40% of those of Iowa. As rates are set on the basis of dollar loss, why the differences? Some states with legislative limitations on awards have lower rates than the mean. In other low-cost states without this limitation on awards, is the practice of anaesthesia of higher calibre, are risk management programmers better, plaintiffs' lawyers less aggressive, or are judges and juries less liberal? The answers to these questions might be of interest, but it may be just a matter of time before the low-cost states catch up with their more expensive neighbours.

The 1986 rates represented a 37% increase over 1985 rates, and no end is in sight. It should be noted that, in general, the private and physician-owned companies have approximately the same cost of coverage.

The related problems of high medical liability awards and increasing cost of professional liability insurance are spreading across the border from the United States to Canada. In 1985 a $1.9 million court award was reported in Canada for anaesthesia-related brain damage after a sterilization procedure (Walt, 1985). At the time, this was thought to be the largest medical malpractice award in Canadian history (Walt, 1985). This record was short-lived, as it was soon followed by a $2.2 million award for anaesthesia-related brain damage sustained during thyroidectomy (Walt, 1986a). Professional liability premiums for Canadian anaesthetists were $4900 per year in 1986 and increased to $8250 in 1987. By comparison, the same amount of coverage cost $500 in 1983 (Walt, 1986b).

The health care industry is not the only provider of services affected by high liability costs. Because of the high cost of legal defence, increased numbers of law-suits, and increased dollar awards, such diverse entities as municipalities, schools, daycare centres for children, chemical companies, financial institutions, oil companies, pharmaceutical companies, the transportation industry and small businesses have all experienced soaring liability premiums. In some cases, insurance coverage has become unavailable at any cost. Product liability has become a major concern to manufacturers of pharmaceuticals in the United States (Hilder and Wynter, 1986) and, more specifically, manufacturers of anaesthesia and critical care equipment are severely affected. Liability awards against the U.S. Government itself have reached epidemic proportion in regards to both numbers and cost (Kurtz, 1985).

Legal background

The American way of resolving disputes is the adversarial approach, in which the courtroom is the final resort. Professional liability of malpractice falls under the tort system. A tort is defined as a civil wrong that one person commits against another and for which the courts grant compensation via the legal process. Under the tort system a physician is usually sued for "negligence" by the aggrieved patient. To establish negligence, the plaintiff must prove four elements:

(1) *Duty*—the physician "owed" the patient a certain "standard of care".

(2) *Breach of duty*—the physician violated the standard of care.

(3) *Causation*—there was a causal connection between the physician's acts and the injury.

(4) *Damages*—physical, financial, or emotional injury occurred to the patient or relatives.

Duty to the patient is established when a doctor–patient relationship exists (Peters et al., 1983). When the patient is seen before operation and the anaesthetist agrees to provide anaesthesia, or when an anaesthetist agrees to "take call" for emergencies, a duty to the patient is established. The duty owed to patients is to adhere to the "standard of care" for treatment of the patient. Since no specific standards for all aspects and contingencies of medical practice exist, the courts have created the concept of the "reasonable and prudent" practitioner (Peters et al., 1983). For all specialties there is a national standard such that the physician is held accountable according to what any reasonable and prudent anaesthetist anywhere in the United States would do in the same or a similar situation. The court establishes the standard of care in a particular case by the testimony of "expert witnesses". To determine whether a *breach of duty* occurred, expert witnesses review the medical records of the case and opine whether the individual acted as a reasonable and prudent anaesthetist in a specific situation. If the plaintiff's experts establish to the jury's satisfaction that the anaesthetist did something below standard, then the breach of duty requirement for a successful suit will have been met.

Causation must be proved by the plaintiff by presenting evidence that the defendant's action was the most likely cause of the injury (Peters et al., 1983). While the burden of proof is usually on the plaintiff, under special circumstances it may be shifted to the defendant under the doctrine of *res ipsa loquitur*. This means essentially that "the thing speaks for itself", and in order for the doctrine to be applied the injury must be a kind that would not occur in the absence of negligence. The injury must be under the exclusive control of the physician and the patient must not have contributed to the injury. Because patients under general anaesthesia are under the exclusive control of the anaesthetist for anaesthesia-related events, the doctrine might be invoked in anaesthesia cases more than in others. This doctrine would be applied, for example, if the patient were allowed to fall off the operating table while anaesthetized.

In order to receive compensation, the patient must prove that *damages* were caused by the physician's negligent act. Three types of damages may be asked for: *general*, *special* and *punitive or exemplary* damages (Peters et al., 1983). General damages are those such as pain and suffering, which result directly from the injury. Special damages are the actual costs, such as past and future medical expenses, lost income or funeral expenses. Punitive or exemplary damages make up a third category. Punitive damages are intended to punish the physician for negligence, and exemplary damages are awarded to make an example of the case rather than to punish the defendant (Peters et al., 1983). As anaesthesia-related injuries often lead to brain damage or death, their economic cost is often quite high. Plaintiffs' attorneys work on a contingency fee basis, claiming a percentage of the award (usually 30–50%) plus the expenses of pursuing the case. The problem with the contingent fee is that, if only actual economic loss is awarded, there will be a net loss because the patient must pay 30–50% of the award to the lawyer. Therefore, in order to receive full compensation for economic damages, injured patients have to obtain a substantial amount from either the general (pain and suffering) or punitive damage category.

The vast majority of claims against physicians are settled before going to court. The author has reviewed over 100 anaesthesia- and critical care-related cases in the past 7 years, only four of which have ever gone to court for final settlement.

One of the major problems with the tort system, from the physician's point of view, is that the rules and regulations of the legal system are an entirely foreign way of dealing with problems. For example, the "standard of care" is not set by the physician's recognized peers or specialty organizations, but rather by a lay jury responding to "expert witnesses" retained by either side. Too often the "standard of care" will depend upon the showmanship and communication skills of the individual "expert" rather than the scientific validity of his or her opinion. Often in anaesthesia-related injuries, even conscientious, knowledgeable experts will take the position that, while there is no evidence of substandard care, the outcome (injury) is unlikely unless some breach occurred in the "standard". This stance puts the burden of proof on the defendant to show that the care met the "standard". This willingness of experts to declare negligence on the basis of bad outcome may be unnecessarily harsh, as it suggests that medical science knows all there is to know about the effects of drugs and procedures on the human body. Keats (1979) has emphasized that all mortality and morbidity from anaesthesia is not preventable. Before knowledge of such syndromes as malignant hyperthermia and suxamethonium-induced hyperkalaemia, mortality and morbidity related to these syndromes might have been ascribed to a breach of the standard of care (Keats, 1979).

What characteristics define an expert witness is unclear, for no national guidelines or definitions exist. Any anaesthetist, regardless of training or board certification, can serve as an expert witness in an individual case. In the medical field there is aggressive commercial marketing of expert witness services, with advertisements in both medical and legal journals (Walt and Golin, 1985). The opinions of experts may have far-reaching effects on both sides, yet there is no true peer review of the accuracy of expert testimony. Millions of dollars may change hands on the basis of the testimony of one or two "experts" who may be considered expert only by their own proclamation.

Another problem with the tort system is that it is extremely expensive. Good defence attorneys are very painstaking, their hourly rates are similar to those of anaesthetists, and for the plaintiffs' attorneys there is the contingency fee. Not surprisingly, less than half the liability dollars paid out by the insurers ever reached the injured parties (Walt and Golin, 1984a). While the contingency fee arrangement at first glance would seem to be a major villain in the professional liability problem, it does have certain merits. The main characteristic of this type of arrangement is that if financial recovery is not obtained, the lawyer receives no fee from his client. Therefore, this arrangement allows economically disadvantaged individuals access to legal services (Ottensmeyer, Smith and Porter, 1983). The system also forces the plaintiffs' attorneys to screen the cases they wish to pursue through ~~the tedious~~ litigation process, as they do not want to waste time on cases for which there will be little or no economic recovery. This screening process by plaintiffs' attorneys does, to some extent, reduce the number of claims. Although the defendant wins in 60–70% of verdicts in cases which actually go to trial, the average award is quite high in those cases in which the plaintiff prevails. In 1983 in California, 49 plaintiffs' verdicts yielded an average award of $649210 (Walt and Golin, 1984a). The possibility of a high jury award has the effect of inflating settlements which are made to avoid having a case go to court. Finally, if cases do go to court, their final settlement may occur years after the original injury. For example, in a case in which the author participated as an expert witness, the injury was a cardiac arrest occurring in early 1980 and a defence verdict was reached by jury trial in late 1982. However, the verdict was overturned by an Appeals court in 1985 and a new trial scheduled for late 1987, more than 7 years after the event. Final resolution of the case may take 8 years or more.

Why are anaesthetists high-risk?

Anaesthetic injuries are high-cost injuries. Awards and jury verdicts in the millions of dollars are not uncommon. Death and brain damage do occur as a result of anaesthesia, even in the absence of negligence (Keats, 1979). About 2000 of the 20 million patients undergoing general anaesthesia in the U.S. are estimated to die each year as a result (Nagel et al., 1985). Anaesthetists depend heavily upon machines which can fail, and perform high-risk interventions which may have significant side effects. They also use potent drugs with which mistakes in dose or labelling can lead to disastrous results. Vigilance, which is the highest priority item in anaesthetic practice, is often difficult to maintain through long, tedious surgical procedures.

A major problem inherent in anaesthesia is that physician–patient relationships are often weak or non-existent: the patient does not usually choose the anaesthetist, the preoperative visit is brief, and the patient's awake contact with the anaesthetist is also usually brief. Sometimes one anaesthetist performs a preoperative visit, another anaesthetizes the patient, and a third may perform the postoperative visit. Even if the anaesthetist sees before operation a patient whom he expects to anaesthetize, when the surgical schedule changes, priority is always in favour of having the same surgeon attend the case, rather than the anaesthetist who made the preoperative visit. Anaesthetists and surgeons do not always communicate well with each other about complications, and some surgical colleagues may tend to blame anaesthesia.

Supervision of nurse anaesthetists is a problem unique to the United States. A ratio of one anaesthetist to four nurse anaesthetists has been established by the federal government as the lowest staffing ratio for which an anaesthetist can receive payment under the federal health systems (Medicare, Medicaid). For medico–legal purposes, however, no standard exists other than the "reasonable and prudent practitioner". Adequate supervision is usually understood to mean physical presence of the anaesthetist in the operating room during high-risk portions of the procedure (e.g., induction and emergence) and immediate availability if any event requiring physician intervention occurs during the course of the anaesthetic. The number of nurse anaesthetists supervised at a given time will, therefore, depend upon the complexity of the case, the patient's physical condition, and the experience of the nurse anaesthetist. Liability insurers in many parts of the United States have set standards for the number of nurse anaesthetists who can be covered by the insured anaesthetist. In 1984 some insurance companies specified a staffing ratio of 1:2 or 1:3 and charged higher rates for supervision of more than that. If data accumulate showing that low staffing ratios of anaesthetists to nurse anaesthetists has an adverse impact on losses, then more liability insurers are apt to specify staffing ratios. It should be pointed out that the anaesthetist is liable, not only for the nurse anaesthetists who are in his employ, but also for the actions of nurse anaesthetists employed by the hospital. If a hospital-employed nurse anaesthetist has a complication, the supervising anaesthetist will most certainly be named as a defendant in the suit.

One other medico–legal hazard to which the anaesthetist is exposed is the shotgun approach used by plaintiff's attorneys in which all those involved in the care of a patient with an adverse outcome are named in an action. As the anaesthetist may care for patients undergoing high-risk surgical procedures, if an injury occurs as a result of the surgery, the anaesthetist will commonly be named in the complaint, whether or not there is any probability of anaesthesia contributing to the injury.

Finally, the mass media have directed a great deal of attention in recent years to anaesthetic mishaps. Television exposés and newspaper coverage have heightened the public's awareness of the serious injuries that may result from anaesthetic mishaps.

What is being done

A Special Task Force on Professional Liability and Insurance of the American Medical Association (AMA) has studied the problem (Walt and Golin, 1984a, b) and proposed some solutions (Walt and Golin, 1985). The Task Force made recommendations in four broad areas: education and community action; legislation; defence co-ordination; and risk control and quality review activities (Walt and Golin, 1985).

The task of educating the public is being performed in a number of different ways, ranging from preparation of material for distribution to individual patients, so enlisting the co-operation of health care coalitions composed of opinion leaders and policy-makers to address the professional liability problem. The AMA is also working closely with other groups which are heavily affected by the high cost and limited availability of liability insurance. The AMA also serves as a clearing house in assembling data, legislative information, materials from specialty organizations, and other materials to share with physicians, medical organizations, coalitions, legislators, policymakers, and other groups affected by the problem.

On the legislative front, the AMA is working for legislative and judicial reform which will not only mitigate the crisis, but also efficiently ensure fair and adequate compensation for injuries arising from medical negligence. This effort is being carried out at both the Federal and State levels. The AMA has established a professional liability clearing house which provides a central information resource and co-ordination system for data collection and research studies on liability issues. A monthly newsletter (*Professional Liability Update*) provides current information on legislation, court decisions, research, and AMA and medical society activities in the liability field. The AMA also recognizes the need to educate physicians more fully about their liability exposure, and that courses are required at both the undergraduate and postgraduate levels (Walt and Golin, 1984b). In addition, the AMA supports expanding peer review and strengthening of State Licensing Boards in order to weed out incompetent physicians.

Other organizations working on the professional liability problem include the Physician Insurers Association of America and the Council of Medical Specialty Societies.

The American Society of Anesthesiologists has two committees involved in the professional liability area. The Committee on Patient Safety and Risk Management is concerned with minimizing patient injury from anaesthesia-related activities. This Committee has developed videotapes on problems in anaesthesia, such as: Anaesthesia Checkout, Disconnection, Proper Anaesthesia Records, Management of an Adverse Event, and Human Errors in Anaesthesia. The Committee is concerned with effecting changes in anaesthetic practice which will improve patient safety. The Patient Safety Committee, therefore, is dedicated to preventing patient injury, which should in turn reduce the number of claims. The Committee on Professional Liability, on the other hand, is essentially concerned with what happens after patient injury occurs. Its major activity at present is collection of data on adverse events in anaesthesia, from insurance company files of claims that have been closed. These data are being gathered from a number of sources, with the goal of identifying the major causes of anaesthesia-related claims. On the basis of this information, it is hoped that changes in behaviour and in anaesthetic systems may help to improve patient safety. Both ASA Committees are involved in an intensive effort to educate the membership about the problems involved with professional liability.

The Anesthesia Patient Safety Foundation was organized in 1985 by Dr Ellison C. Pierce, a past president of the American Society of Anesthesiologists, who has been a leader in the field of patient safety in anaesthesia. The organization, which is independent of the ASA, was founded to improve the safety of patients undergoing anaesthesia. Fifteen of the 30-member Board of Directors of the organization are anaesthetists. Other members of the Board include representatives of equipment manufacturers, pharmaceutical firms, the Federal Drug Administration, medical liability insurance companies, and the Director of the Risk Management Foundation at the Harvard hospitals. The Foundation publishes a newsletter and supports clinical research directed towards enhancement of patient safety.

On the local level, legislative relief (tort reform) in the individual states has had varied success since the first laws were enacted in the mid-1970s (Walt and Golin, 1984b). The major reforms which have been adopted in different states are pre-trial screening panels, the collateral source rule, attorney fee regulation, statute of limitation changes, limitations on liability, and periodic payment of damages (Walt and Golin, 1984b).

The pre-trial screening panel is composed of physicians, lawyers, and laypersons who review claims and render decisions as to their merit. If a claim is found to have merit, either the plaintiff or the defendant can then pursue a jury trial. One important feature is whether panel review is made mandatory or not. With mandatory review, the number of claims may be reduced, but the law requiring panel review may be found unconstitutional. In the 30 states in which this law was originally adopted, pre-trial panels have been upheld by 10 State Supreme Courts, struck down by four, and repealed by four other state legislatures (Walt and Golin, 1984b).

The collateral source rule prevents a jury from learning that a plaintiff has been compensated for the injury from another source, such as life insurance, health insurance, or workers' compensation. In this way the plaintiff may receive double compensation for his injuries. In 19 states, legislation has been enacted to limit this excess recovery.

Regulation of attorney's fees, an issue emotionally satisfying to most physicians, has been enacted in 23 states. Whether this limitation will reduce the number or severity of suits is unclear, but ideally more of the money awarded will be recovered by the injured party.

Statute of limitation change is the common tort reform, adopted now in 40 states. The time after the event during which a plaintiff can bring action is shortened, limiting the length of the "tail" which has been such a problem for insurance companies in forecasting future costs. In general, state legislatures have changed the laws to require initiation of action within 2 years after the injury, or 2 years after the injury should have been discovered. These limitations do not apply to minors: thus a problem remains for those involved in obstetrics and paediatrics.

Limitations on liability either put a ceiling on the amount of money a jury can award for "non-economic damages", or limit a physician's liability to a fixed amount. No limit is placed on actual losses for medical expenses or wages. Limitation of awards against physicians is usually tied to a patient compensation fund within the state. Under this system, awards over a certain amount ($100000–300000) are paid out of a state-operated fund into which all physicians pay. In states such as Indiana, which place an absolute limit on physician liability regardless of the circumstances, no award for medical liability may be greater than $500000 (Walt and Golin, 1984b). California's 10-year-old law, which limits *non-economic* damages to $250000, has recently been held constitutional by the State Supreme Court. The financial impact of this law will not be known, therefore, for several more years.

Periodic payment of damages calls for the paying out of awards in instalments rather than in a lump sum. This approach reduces the initial cost and the insurance company's liability if the patient subsequently dies earlier than predicted.

At the Federal level, two approaches are currently being considered by the Congress in an attempt to ease the professional liability crisis. One is a no-fault medical-liability insurance bill, which creates incentives for health care providers to escape potential liability for non-economic damages by offering to pay a patient's economic losses. This bill would make it easier for patients to recoup economic losses resulting from adverse medical outcomes, but it would bar compensation for "non-economic" losses. This Federal law would apply only to claims arising from Federally-funded health services, such as Veterans Administration, Medicare and Medicaid. This approach has not been widely supported by organized medicine, because the cost of such a system is unknown. Clearly, the definition of a "compensatable injury" would become a critical issue. Other approaches, including a bill sponsored by the AMA, would provide financial incentives for states to enact tort reform.

The insurance industry has become active in the field of controlling professional liability rates. The Physician Insurers Association of America has a computerized data collection system, which helps identify the causes of claims, and also identifies new trends in professional liability. Knowledge about why physicians are sued should lead to remedial action. This type of information-gathering may lead to "restrictive endorsements" on professional liability insurance policies. Several physician-owned insurance companies have imposed guidelines for anaesthetists which must be met for their professional liability insurance to apply (see below). Undoubtedly, these steps are only the beginning of this type of activity by insurance companies.

What should the individual anaesthetist do?

The individual anaesthetist should practice "defensive medicine". The making of pre- and postoperative rounds, developing good patient relationships, and maintaining up-to-date practice habits are essential. Good records can form a strong defence if they are adequate, and can be disastrous if inadequate. Informed consent should be documented with a general consent. In addition, there should be a note in the patient's record that the risks of anaesthesia and alternatives were discussed and that the patient accepted the proposed anaesthetic plan. A brief documentation in the record that the common complications of a given technique were discussed is helpful.

The anaesthesia record itself should be as accurate, complete and neat as possible. Sloppy, inaccurate anaesthesia records enlarged and placed before a jury for the duration of a trial lasting days to weeks do not help the defence. If a critical incident occurs during the conduct of an anaesthetic, the anaesthetist should document in narrative form in the patient's progress notes what happened, which drugs were used, the time sequence, and who was present. Attempts to summarize a catastrophic intra-anaesthetic event in a small amount of space on the usual anaesthesia record are simply inadequate. The critical incident note should be written as soon as possible, while all the details are fresh. The critical incident report should be as consistent as possible with concurrent records such as the anaesthesia, operating room, recovery room and cardiac arrest records. If inconsistencies exist, they should be explained in the critical incident note. Again, litigation is a lengthy process, and a court appearance to explain the incident to a jury may be years away when memories have faded. If anaesthetic complications occur, the anaesthetist should be honest with both the patient and family about the cause. Consultations should be obtained quickly from the appropriate consultants and the patient should be followed closely while in the hospital with telephone follow-up, if indicated, after discharge. Also, the anaesthetist and the surgeon should be consistent in their explanations to the patients as to the cause of any complication.

While it may seem obvious, qualified anaesthesia personnel should be in continuous attendance during conduct of all anaesthetics. The only exceptions should be those which lay people (i.e., judge and jury) can understand, such as radiation hazards, x-ray, or an unexpected life-threatening emergency elsewhere. Even then, provisions should be made for adequately monitoring the patient. Anaesthetic complications occurring while anaesthesia personnel have left the room without urgent reason are indefensible and command very high financial settlements or court awards.

Adequate supervision of nurse anaesthetists and residents and good communication with surgeons when adverse anaesthetic outcomes occur are also important. On a department level, an ongoing process of concurrent record review based on established standards of care criteria, and anaesthesia-related morbidity and mortality should be reviewed regularly. A regular schedule of equipment maintenance and procedures to follow in cases in which equipment malfunction is suspected of contributing to patient injury should be established. If equipment malfunction is suspected to have contributed to a complication, the device should be impounded and examined by representatives of the hospital and manufacturer. The use of checklists before each case, or at least daily, should reduce equipment-related mishaps (Spooner and Kirby, 1984).

Role of monitoring in reducing patient injury

Adequate monitoring would seem to be one of the more critical factors in preventing patient injury from anaesthesia. Physiological monitoring of cardiopulmonary function, combined with monitoring of equipment function, might be expected to reduce anaesthetic injury to a minimum. Equipment monitors are designed to detect serious equipment failures before harm to the patient. Monitoring is receiving a great deal of attention for several reasons. In any analysis of anaesthetic mishaps, it is common to see that many could have been prevented by the use of an appropriate monitor. Another reason for the focus on monitoring is that technology is available to monitor both the relevant mechanical functions of the equipment and the physiological functions of the patient. As manufacturers stand to profit from widespread sale of monitoring equipment, industry then emphasizes the role of monitoring in prevention of patient injury. The urgent need to "do something" to reduce anaesthesia-related injuries and the availability of monitoring technology make monitoring the current focus of the patient safety issue.

While everyone would agree that the adequacy of oxygenation, ventilation and circulation should be monitored during all anaesthetics, the means to do so may be controversial. The standards of practice for monitoring functions have evolved in a number of different ways in the United States. One way monitoring standards have developed is a general consensus among practitioners that a particular monitor is useful. For example, arterial pressure measurement by cuff would fall into this category. This mode would seem to be the least controversial avenue for the development of standards, but unfortunately technology, medical science and legal theories of liability are changing so rapidly that the profession does not have time to develop a general consensus over a long period of time.

Another way in which standards of practice come into being is as a result of jury verdicts. An example cited by Rubsamen (1984) is the development of constant heart rate monitoring as a standard of practice in California in the 1970s. A $1.4 million verdict was rendered against a California anaesthetist in a 1973 case in which a 37-year-old female had a cardiac arrest during a brief elective procedure. The plaintiff's expert testified that the anaesthetist should have been monitoring the heart rate constantly. In spite of ample defence testimony that constant heart rate monitoring was not community standard, the jury ruled for the plaintiff. Over the next 2 years, four more cases in California involved the issue of constant heart rate monitoring, and each resulted in an award against the anaesthetist defendant. Because of these awards, constant heart rate monitoring, no matter how routine or brief the anaesthetic, became the standard of practice throughout California (Rubsamen, 1984).

Recently, professional liability insurers have entered the picture by setting monitoring standards themselves. Their behaviour in this regard is a reaction to the escalating costs of compensation for patient injury. Standards for minimal monitoring have been set by several physician-owned insurance companies in the West and Southeast U.S.A. These "standards" or "guidelines" have been imposed in the form of restrictive endorsements on professional liability policies which itemize the monitors that should be in use during the conduct of an anaesthetic. If claim arises in which the monitoring guidelines are not met, the anaesthetist is not covered. In general, these guidelines cover such details as physical presence during the conduct of an anaesthetic, and the use of such monitors as precordial or oesophageal stethoscope, ECG and arterial pressure cuff.

Another example of how the liability issue has affected the development of monitoring standards is the experience of departments of anaesthesia in the Harvard (University) hospitals. Analysis of anaesthesia-related incidents at the nine component hospitals and subsequent malpractice litigation led to the establishment of "standards for minimal monitoring" during the conduct of an anaesthetic. As with the insurance company guidelines, these standards call for continuous presence of the anaesthetist, and for monitoring of arterial pressure, heart rate and ECG. In addition, the standards specify breathing system disconnect monitoring and monitoring of the oxygen concentration during general anaesthesia. These standards also state that end-tidal carbon dioxide analysis is an "emerging standard" for monitoring ventilation and is "strongly preferred".

In 1986 the American Society of Anesthesiologists adopted standards for minimal monitoring which are similar to the Harvard standards. Many anaesthetists would argue that official standards are restrictive and ignore the judgement and experience of the individual practitioner in the use of alternative methods of monitoring oxygenation, ventilation and circulation. On the other hand, with insurance companies and hospitals setting their own standards for monitoring, it would seem reasonable for organized anaesthesia (i.e., the ASA) to provide leadership in the endeavour.

The author's opinions of monitoring and its role in patient safety have been developed from 22 years of university practice, 7 years of activity as an expert witness for both plaintiffs and defendants, and as Chairman of the ASA Committee on Professional Liability. (The opinions expressed are those of the author and do not represent those of the American Society of Anesthesiologists.) As noted above, the ASA Committee is conducting an in-depth review of anaesthesia-related insurance company closed claims from various areas of the United States and, of 350 cases reviewed to date, 31 oesophageal intubations resulted in brain damage or death. In 19 of these 31 cases, auscultation of the chest was documented in the record. These cases imply that auscultation of the chest is not a universally satisfactory method to ensure correct placement of a tracheal tube. Measurement of end-tidal carbon dioxide concentration immediately following insertion is a more accurate method of assessing correct tracheal tube placement, and perhaps should be adopted as a standard of practice (Birmingham, Cheney and Ward, 1986). This is the standard of care at the University of Washington hospitals, not only in the operating rooms and obstetric suites, but also in the Critical Care Center of the University of Washington Hospital (Owen and Cheney, 1985).

Another area in which current standards leave much to be desired is the practice of bilateral chest auscultation to ensure that a tracheal tube is not lodged in the bronchus of one lung. The author has seen numerous instances in which breath sounds have been recorded as present bilaterally, yet there is x-ray evidence of endobronchial intubation with atelectasis of one lung. Plaintiffs' attorneys are aware that breath sounds are a poor way to rule out endobronchial intubation, and this has been used as a theory of causation in cases of otherwise unexplained hypoxic brain damage (Rubsamen, 1985). The problem of endobronchial intubation can easily be solved with the use of tracheal tubes with centimetre markings on the side. Positioning an oral tracheal tube 21 cm at the teeth in normal-size females and 23 cm in normal-size males would virtually eliminate the problem. We have not seen x-ray evidence of an endobronchial intubation in patients in whom this practice was carried out since adoption of this standard 2 years ago in the Critical Care Center of the University of Washington Hospital. In nasal intubation or oral intubation of patients of other than normal adult size, the tracheal tube should be measured from the sternal notch to the nare or from the sternal notch to the teeth before placement, as suggested by Dornette (1963).

There is also a need for improved practice in monitoring the adequacy of ventilation during regional anaesthesia. The combination of sedation and regional anaesthesia, especially spinal anaesthesia, has been associated with morbidity (brain damage) and mortality, with disturbing frequency. The precordial stethoscope is a common method of monitoring ventilation in this setting, but suffers from the drawback of being non-quantitative. Pulse oximetry may be a partial solution, but if the patient is receiving oxygen during regional anaesthesia, hypercapnia may engender deleterious cardiovascular effects before significant desaturation occurs. A simple quantitative or semiquantitative monitor of ventilation is needed for the patient who is not connected to an anaesthesia circuit by mask or tracheal tube.

In the author's opinion, general standards for minimal monitoring during anaesthesia should consist of the following. For monitoring oxygenation, an oxygen analyser should be used if general anaesthesia is administered. Monitors of ventilation should include precordial or oesophageal stethoscope, a spirometer if general anaesthesia is used, and a disconnect alarm if mechanical ventilation is in use. Circulatory monitoring should include a precordial or oesophageal stethoscope, ECG and arterial pressure cuff for all anaesthetics. In addition, temperature monitoring should be available and utilized where appropriate, such as where significant increases or decreases in temperature may be expected. End-tidal carbon dioxide monitoring and pulse oximetry, while perhaps not minimal standards at present, should be considered as optimal and will probably become standard practice in the U.S. in the foreseeable future.

SUMMARY

The professional liability climate in the United States can best be described as tempestuous in most areas of the U.S. The major strategy of organized anaesthesia and the professional liability insurance industry is to attempt to reduce patient injury. In the unlikely eventuality that human error and equipment failure in anaesthesia can be eradicated, some patient injury will inevitably still occur. For this reason tort reform is necessary, and alternatives to the tort system need to be developed to compensate injured parties adequately without bankrupting the medical system.

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ESSENTIAL MONITORING

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In the early days of anaesthesia the anaesthetist observed the heart rate, the pattern of breathing and the patient's response to surgery. Later, the signs indicating depth of anaesthesia were recognized. The recording of arterial pressure during operation was introduced at the beginning of this century, but there were no further significant developments in monitoring until after the Second World War. The initial stimulus for the development of new techniques was the introduction of controlled ventilation for thoracic surgery. This was followed by the increasing use of methods of controlling the circulation (e.g. induced hypotension) and the development of cardiac surgery with its associated techniques of hypothermia and cardiopulmonary bypass.

With the improvements in technology and developments in the intensive care field, monitoring has now become routine. However, there have been no controlled trials to determine whether monitoring has produced a significant improvement in patient outcome (Pace, 1985). The paucity of studies in this field and the immense pressures generated by the upsurge of medico–legal activity have resulted in an explosive increase in the use of monitoring in the United States. Since the United Kingdom is now beginning to experience similar pressures, it is appropriate to attempt a critical appraisal of current techniques, to try and determine which monitors may be considered essential.

The anaesthetist performs five major functions during surgery. These are: administration of drugs to secure unconsciousness, analgesia and muscle relaxation; maintenance of the airway and the provision of adequate ventilation with humidified gas mixtures containing the appropriate concentrations of oxygen; maintenance of blood volume, adequate functioning haemoglobin and a satisfactory circulation; maintenance of renal function with control of fluid and electrolyte balance, acid–base balance and deranged metabolic functions (e.g. control of blood sugar); and control of temperature.

Thus, safety in anaesthesia can only be achieved by monitoring the performance of the anaesthetist, the function of the apparatus used to give the anaesthetic, the patient's response to anaesthesia and surgery, and the performance of the monitoring apparatus used to carry out these tasks.

At the present time, monitoring falls far short of this ideal. There are several reasons for this state of affairs. First, the major source of anaesthetic-related morbidity and mortality is human error: until we can devise a means of monitoring the performance of the anaesthetist this will continue to be a major problem. Second, the monitors currently available are not capable of performing the appropriate measurements. The two major requirements in anaesthesia are the abilities to monitor brain cell biochemical function and the depth of anaesthesia: in the present state of the art neither can be monitored satisfactorily. Third, the reliability of most monitors is less than optimal because of problems with the transducer–patient interface and poor artefact rejection. The lack of reliability not only discourages anaesthetists from using monitors, but may create a positive hazard for the patient, for an anaesthetist who is trying to find the cause of a monitor failure is likely to be distracted from the care of the patient.

MONITORING THE ANAESTHETIST

Studies of morbidity and mortality and critical incident analysis have revealed that the majority of complications associated with anaesthesia result from inadequate training or inadequate experience of the anaesthetist (Cooper et al., 1978; Craig and Wilson, 1981; Lunn and Mushin, 1982; Cooper, Newbower and Kitz, 1984). Some are caused by tiredness or boredom, and others by lack of attention. Knowledge and experience are a function of the intensity and duration of training,

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but vigilance is, unfortunately, only generated by self-motivation. However, a higher degree of vigilance can be induced by continually stressing hazards during training, and by encouraging assistants to be closely involved with the giving of the anaesthetic.

An interested assistant can do much to warn the anaesthetist of malfunction of the apparatus or changes in the patient's condition. A well-trained O.D.A. or nurse should monitor the patient's heart rate during intubation, watch the rotameters and the movements of the reservoir bag or ventilator pressure gauge whilst the anaesthetist is setting up an i.v. infusion or is otherwise distracted, and should ensure that an efficient suction apparatus, emergency drugs and resuscitation fluids are readily available in the theatre before surgery commences.

The surgeon can also help to maintain the alertness of the anaesthetist by showing an interest in the patient's condition and by communicating with the anaesthetist when blood loss is anticipated or observed.

Above all, it is necessary for the anaesthetist to monitor him/herself. Procedures should be developed to ensure that every aspect of apparatus function is checked before use, and similar check lists should be applied to the execution of common procedures. There would be no unrecognized intubation of the oesophagus, or a major bronchus, if the anaesthetist listened to the breath sounds *in each* axilla after *every* intubation, whilst hypoxic incidents as a result of oxygen supply failure, disconnection or a deflated tracheal tube cuff would be eliminated by the routine use of inspired oxygen concentration and expired volume monitors in every patient. One major source of trouble, an inadequate supply of fresh gas, resulting from the failure to turn on the fresh gas supply, a leak in the anaesthetic machine or a disconnection between the common gas outlet and the ventilator or breathing system, can only be detected with certainty by inspired oxgen concentration, end-tidal carbon dioxide concentration and expired volume monitoring; however, it can usually be avoided by ventilating the lungs manually before switching on the ventilator. It is the failure to carry out these simple checks in every case which is the greatest single cause of anaesthetic disaster. If an airline pilot fails to carry out such checks, he is severely reprimanded or dismissed; the same discipline should be applied to anaesthetists.

Finally, every encouragement should be given to anaesthetists to follow the patient's progress after operation. A record of the postoperative analgesic requirements, and the incidence of nausea, vomiting and other major and minor complications, provides a good corrective to slipshod practice. The fact that final F.F.A.R.C.S. candidates frequently display complete ignorance of the incidence, duration and therapy of postoperative complications suggests that this aspect of training requires much more attention.

MONITORING APPARATUS FUNCTION

It is necessary to consider: first, devices used to administer drugs i.v.; second, the apparatus used to provide a respirable gas mixture containing the appropriate concentrations of oxygen, nitrous oxide and anaesthetic vapours; third, the breathing system used to transmit this mixture to and from the patient; and fourth, the apparatus used for mechanical ventilation of the lungs.

I.v. infusion apparatus

This apparatus may be classified into two categories: the infusion controllers which use gravity to drive the fluids into the vein, and piston or roller pumps which are motivated by clockwork, pneumatic or electrical power. These devices should be designed so that they display a warning when the prescribed dose rate is not being given, and there should also be an indication when the reservoir or syringe is emptied. In the case of mechanized pumps, it is important that there should be an alarm to indicate high pressure in the delivery line secondary to an obstruction. Air embolus is another major hazard which should be guarded against, particularly in neonates and other patients with a potential or active right-to-left shunt.

The anaesthetic machine

The purpose of the anaesthetic machine is to supply an adequate flow of fresh gas containing at least 21% oxygen to a breathing system or ventilator. However, when considering monitoring requirements, it is necessary to consider the interactions between the machine, breathing system and patient, for successful monitoring can only be achieved by integrating the monitoring system with the design of the anaesthetic machine.

It is important to remember that there are often significant time delays between an alteration in fresh gas or vapour concentration and a change in the patient's condition; these are caused by the presence of large volumes of gas in the breathing system and the lungs, and by the time required to transfer blood from the lungs to the tissues. The delay will be minimal when the fresh gas is delivered directly to the patient through narrow bore tubing, as in the Bain breathing system. It will be increased significantly if a breathing system or ventilator with a large internal volume is used, particularly if fresh gas flow is low, since the wash-in time constant of the system is determined by the fresh gas flow and system volume. A further delay is introduced by the lungs, the change in alveolar concentration being slowed by a reduced alveolar ventilation or high uptake of oxygen or vapour into the blood, and by an increased functional residual capacity. Finally the rate of change of tissue concentration will be affected by the cardiac output. Thus, a pulse oximeter placed on the ear or finger may not register a change in arterial saturation for several minutes after a failure of the oxygen supply when low fresh gas flows are being used with a circle absorption system (Kerr, 1985). Even if the oxygen supply is restored immediately, there may be a significant delay before gas with an adequate oxygen concentration reaches the lungs. During this period a precipitous decrease in arterial saturation is likely to have occurred, with inevitable cerebral damage.

These considerations indicate that it is essential to provide monitors on the anaesthetic machine which give an immediate warning of dysfunction. (It is also important to disconnect the patient from the machine and to use expired air resuscitation or ventilation with a self-inflating bag to restore the alveolar Po_2 to normal values with the minimum of delay.)

What then are the essential machine monitors? For convenience, these will be classified into those monitoring the fresh gas supply and those concerned with breathing system or ventilator dysfunction.

Fresh gas supply. First, there must be an oxygen pressure failure warning device with a clearly audible alarm which is unlike any other alarm noise commonly encountered in the operating theatre. The alarm should be activated when the reduced oxygen pressure in the supply line decreases to two-thirds or one-half of normal. It should be simple, reliable, automatically tested and activated when the machine is brought into use, and powered by the oxygen remaining in the system. The importance of such an alarm is that it sounds as failure occurs and, therefore, enables immediate corrective action to be taken. It may be supplemented by a device which either cuts off the supply of all the other gases, or reduces their flow in proportion to the reduction in oxygen flow, but such a device should never be fitted without an audible warning device (Memorandum, 1977). The reason for fitting a cut-off device or proportional controller is that continued ventilation with a hypoxic gas mixture produces a more rapid reduction in brain Po_2 than does a similar period of apnoea. When there is an oxygen failure in the presence of continued ventilation, the rate of decrease of alveolar Po_2 depends on the ratio of ventilation to lung volume. It is, therefore, increased when minute volume is high and functional residual capacity reduced, as in anaesthesia with controlled ventilation. Simulation on the McPuff computer model of the ventilatory system (Dickinson, 1977) indicates that, with an FRC of 1.5 litre and a minute volume of 8 litre min^{-1}, brain Po_2 will have reached dangerous values within about 1 min of the cessation of oxygen supply. However, when apnoea occurs in the absence of oxygen failure, two protective mechanisms operate. First, the lungs contain a large reservoir of oxygen which is usually increased by the added oxygen given during anaesthesia. Second, there is an increase in Pa_{CO_2} which increases cardiac output and cerebral blood flow, and shifts the oxygen dissociation curve to the right. As a result, there is an initial increase in brain Po_2, followed by a plateau and a delayed decrease, dangerously low brain Po_2 values being reached only after about 2.5 min when 30% oxygen has been inhaled and the FRC is 1.5 litre.

It is now generally agreed that additional safety is provided by monitoring fresh gas oxygen concentration close to the common gas outlet. An oxygen analyser in this position will detect crossed pipe-lines, incorrect flow control settings, errors in flow measurement from sticking of the rotameter bobbins (dirt, faulty alignment of the tubes, or static electricity), and it will also detect a reduction in fresh gas oxygen concentration resulting from a leak in the oxygen flowmeter. However, the presence of such an analyser may lead to a false sense of security. For example, it is common practice to place an oxygen analyser between the breathing system and the common gas outlet (fig. 1). Such a monitor is subject to the usual problems of the slow response time, possible

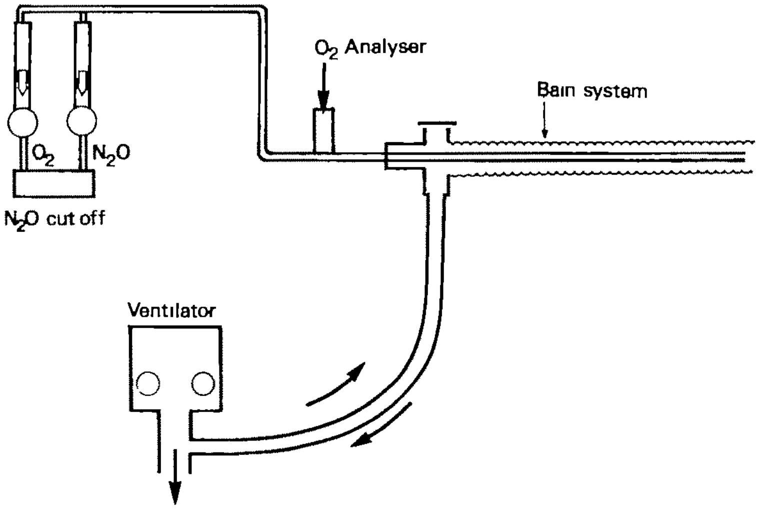

FIG. 1. Misplaced oxygen monitor: An oxygen analyser placed between the anaesthetic machine and Bain breathing system fails to register an oxygen supply failure if the anaesthetic machine is fitted with a nitrous oxide cut-off device. The reduction in fresh gas flow will not be detected by a pressure-operated ventilator disconnect alarm, since the lungs will still be ventilated by the mechanical ventilator attached to the Bain system bag mount.

sensitivity to nitrous oxide or halothane (Severinghaus et al., 1971; Orchard and Sykes, 1980), calibration errors and an increased risk of disconnection at this point. More importantly, it only senses the oxygen concentration in the region of the sensor. If such a device is fitted to a machine which incorporates a nitrous oxide cut-off device, or a proportional controller without an audible alarm, it will fail to give a warning when oxygen failure occurs because the fresh gas flow will be cut off or reduced, whilst the oxygen concentration in the region of the sensor is little changed. When there is a cessation of fresh gas flow into a Bain or circle absorption system used with a mechanical ventilator, there will be some decrease in tidal volume and peak airway pressure, but the ventilator will still produce an increase in airway pressure which will be sufficient to satisfy the lower limit on a pressure-operated ventilator disconnect alarm situated between the breathing system bag mount and ventilator. The patient may thus suffer a severe hypoxic incident even though both monitors are functioning correctly. Other causes of an inadequate fresh gas flow into a breathing system are failure to turn on the fresh gas flow, a leak distal to the flow meters (now increasing in frequency with the widespread use of devices that allow vaporizers to be interchanged), disconnection between the common gas outlet and breathing system, and disconnection within the breathing system itself (e.g. the inner tube of a Bain system).

An inadequate fresh gas supply is easily recognized when a non-rebreathing system is being used because the reservoir bag empties and expired volume is reduced. A reduction in tidal volume is also apparent with a ventilator of the minute volume-divider type (e.g. Manley). However, with other breathing systems and ventilators a reduction in fresh gas flow will result in rebreathing, with a reduction in inspired and alveolar $P\mathrm{O}_2$. In breathing systems without carbon dioxide absorption there will also be an increase in inspired and alveolar $P\mathrm{CO}_2$.

In circle absorption systems the inspired oxygen concentration depends on the fresh oxygen gas and nitrous oxide concentrations and on the relationship between fresh gas flow rate and minute volume. At fresh gas flows equal to, or greater than the minute volume, fresh gas and inspired oxygen concentrations are the same. When fresh gas flow is less than 3–4 litre min^{-1}, the inspired concentration is affected by the relative uptake of oxygen and nitrous oxide into the blood. During the first few minutes of the anaesthetic, nitrous oxide uptake exceeds oxygen uptake, so that inspired oxygen is greater than fresh gas oxygen concentration, but in the later stages of the anaesthetic, nitrous oxide uptake is decreased, so that inspired oxygen is less than fresh gas oxygen concentration. The relationship is fairly predictable at fresh gas flows of more than 2 litre min^{-1} (Forbes, 1972), but at lower flows the effects produced by variations in uptake of the two gases are accentuated. In addition, the accumulation of nitrogen may produce a significant effect (Barton and Nunn, 1975).

There are two other limitations to the use of inspired oxygen monitoring as a guide to the adequacy of fresh gas flow into a circle system. First, there is usually a cyclical variation in inspired oxygen concentration as a result of the mixing of the continuous flow of fresh gas with the intermittent flow of expired gas, a steady inspired oxygen concentration being observed only in systems in which fresh and expired gas are mixed within the reservoir bag before entering the inspiratory tube. Thus, the use of a slow response analyser may yield an inaccurate result. Second, there will be little difference between fresh gas and inspired oxygen concentration if the fresh gas contains only oxygen. It may be concluded that inspired oxygen monitoring can provide a useful warning of the delivery of a hypoxic gas mixture, but is of limited use in detecting an inadequate fresh gas flow into a circle absorption system.

With other breathing systems, such as the Magill, Lack or Bain (Mapleson A or D), there is a to-and-fro movement of fresh gas, deadspace gas and alveolar gas which makes it impossible to obtain a representative sample of inspired gas. Thus, the only infallible monitor of the composition and adequacy of the fresh gas supply is alveolar gas analysis. Unfortunately, this presents technical problems, for whilst infra-red analysers for carbon dioxide are readily available, the only rapid-response oxygen analyser which has been commercially available is the mass-spectrometer. This is expensive, bulky and needs skilled servicing at regular intervals. Since it is not practicable to provide a mass-spectrometer in every operating location, a central mass-spectrometer is often multiplexed to serve a number of operating theatres. The gas samples are transmitted through long, narrow tubes to the central location and two to three breaths are sampled from each patient in turn. Unfortunately, this technique may result in a 15–20 s delay in the analysis of each sample because of the transit time of the sampling system, and a further delay because of the intermittent nature of the sampling. If a 10–15 s sample from each of 12 locations is analysed, this may result in one sampling period every 3 min (Ozanne et al., 1981; Gravenstein et al., 1984). Such a system cannot provide adequate warning of a potential hypoxic incident caused by gas supply failure. Although rapid response polarographic and paramagnetic sensors are now becoming available, experience with their use is limited.

The remaining variable in the fresh gas supply is the concentration of inhalation anaesthetic. When using an oxygen–nitrous oxide mixture, it is usually adequate to measure the oxygen concentration and assume that the balance is nitrous oxide. Such a calculation assumes that there is no dilution by other gases, such as carbon dioxide or air. Fresh gas vapour concentration monitoring has not been much used in the past because of the lack of suitable analysers. However, there are many sources of vaporizer inaccuracy and inspired concentrations in a circle system differ from fresh gas concentrations at low fresh gas flows as a result of pulmonary uptake of the agent (Mushin and Galloon, 1960). Satisfactory rapid vapour analysers are now available and it is likely that these devices will find increasing use for inspired or end-tidal vapour analysis (Ozanne et al., 1981; Luff and White, 1985; Zbinden et al., 1986).

It has been suggested that the analysis of end-tidal vapour concentration could provide a useful guide to the depth of anaesthesia. However, there is serious doubt concerning the validity of this concept. First, the minimum alveolar concentration (MAC) is defined as the minimum concentration which will prevent movement in response to a surgical incision in 50% of patients (Eger, Saidman and Brandstater, 1965). Such a level of anaesthesia would scarcely satisfy our surgical colleagues! Even if the concept is expanded to relate the log of the end-tidal concentration to the probit of the motor response (de Jong and Eger, 1975), there is still a large variation in patient response to a given alveolar concentration. There are several reasons for this. First, there is a variable relationship between end-tidal and arterial concentration (Eger and Bahlman, 1971), probably as a result of variations in deadspace and shunt. Second, MAC is affected by age (Gregory, Eger and Munson, 1969), premedication with opioids (Munson, Saidman and Eger, 1965), the addition of nitrous oxide (Saidman and Eger, 1964) and many other factors (Quasha, Eger and Tinker, 1980). It thus appears that the control of the depth of anaesthesia must still be effected by clinical observation of the patient.

The breathing system and mechanical ventilator. The two major requirements for a breathing system are that it should transmit gases to and from the patient without permitting rebreathing, and that it should vent the waste gases to atmosphere with minimal increase in airway pressure.

Rebreathing is prevented by the provision of an adequate fresh gas flow, the use of valves to separate inspired and expired gas streams, or the use of a carbon dioxide absorber. The difficulties of monitoring the fresh gas supply and inspired oxygen concentration have already been discussed. The detection of rebreathing can be accomplished either by monitoring the concentration of carbon dioxide in inspired gas, or by monitoring alveolar $P\text{CO}_2$ and expired volume. The use of inspired carbon dioxide monitoring can be deceptive, for the reinhalation of gas containing carbon dioxide into the patient's deadspace has no effect on gas exchange. Again, a zero carbon dioxide concentration at some point in the ventilatory cycle does *not* indicate that the inspired gas contains no carbon dioxide (fig. 2). Thus, even if the total quantity of carbon dioxide re-inhaled per breath is measured by relating the instantaneous carbon dioxide concentration to the volume inspired, this may not provide a true indication of the degree of impaired carbon dioxide elimination. Rebreathing is thus best detected by measurement of the end-tidal $P\text{CO}_2$ and expired tidal or minute volume. It is important that both $P\text{CO}_2$ and volume be measured, for some patients respond to an increased carbon dioxide load by increasing alveolar ventilation with little change in end-tidal $P\text{CO}_2$, whilst others develop an increase in $P\text{CO}_2$ with little change in ventilation. The failure to recognize these different responses led to the widespread misconception that the Bain system did not cause rebreathing when used with fresh gas flows of 100 ml kg^{-1} with spontaneous ventilation (Byrick, 1980). When monitoring end-tidal $P\text{CO}_2$ it is important to ensure that a representative sample of end-tidal gas is obtained by sampling within the tracheal tube or the vertical limb of an angled connector. Sampling close to the patient connection port on a Bain system results in marked dilution of the end-tidal gas with fresh gas (Gravenstein, Lampotang and Benekin, 1985).

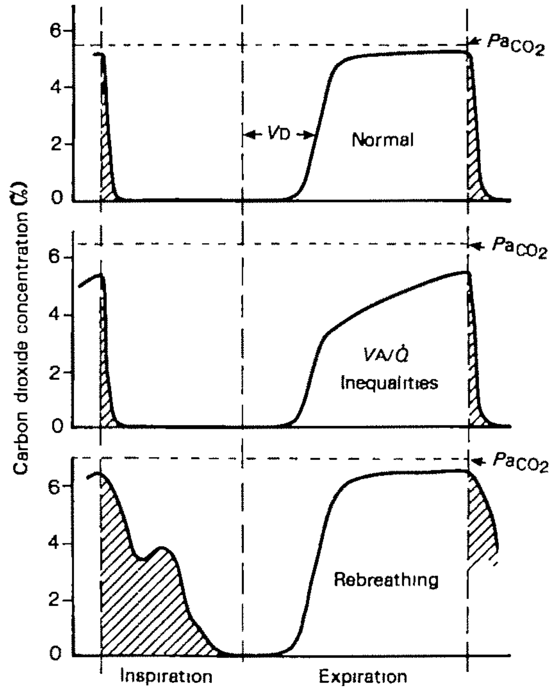

FIG. 2. Carbon dioxide traces recorded from the proximal end of the tracheal tube to illustrate the changed pattern of alveolar plateau in a patient with ventilation/perfusion ($\dot{V}_A/\dot{Q}$) inequalities. Bottom trace shows the presence of carbon dioxide in inspired gas during spontaneous ventilation, although the carbon dioxide concentration decreases to zero during part of the ventilatory cycle.

Leaks within the breathing system are best detected by pressurizing the system before use. A leak between the breathing system and patient can only be detected with certainty by comparing inspired and expired volumes. This necessitates the use of a bi-directional flow meter placed between the patient connection port and the tracheal tube or separate flowmeters in the inspiratory and expiratory tubes of the breathing system. Such a system requires computational facilities and has had limited clinical application to date. However, expired volume monitoring alone provides a reliable method of ensuring that the patient's tidal volume is adequate. The monitor must be situated between the patient and breathing system with a Mapleson A or D system. If it is placed close to the expiratory valve on a non-rebreathing or circle system, two possible sources of error must be considered. One is leakage of gas through the expiratory valve during the inspiratory phase. This can be detected with rapidly responding devices such as the mechanical version of the Wright's respirometer, but if volume is derived from electronic integration of the flow signal and there is no clear zero flow interval between inspiration and expiration, the device may record the total volume of gas eliminated per breath and not the separate inspiratory and expiratory volumes, so that the expiratory valve leak is not detected. The second major source of error is that a spirometer placed close to the expiratory port measures both the volume of gas which has ventilated the lungs and the volume of gas compressed within the breathing system, and any humidifying device included in the circuit. With high inflation pressures, this may result in an overestimate of tidal volume of up to 500 ml when the breathing system volume is large (Loh and Chakrabarti, 1971).

The remaining breathing system hazard is a high airway pressure as a result of inadvertent closure of the expiratory valve, kinking of the expiratory tube, or sticking of a one-way valve in the breathing system. Present safeguards against the dangers of high airway pressure are quite inadequate, for even though safety blow-off valves may be incorporated to the breathing system, these are seldom connected to any audible alarm (Newton and Adams, 1978). As a result, the pressure may build up to the blow-off valve set pressure without any warning being given. Whilst the lungs may be protected against rupture from excessively high pressures, the increased intrathoracic pressure may have a disastrous effect on cardiac output unless the hazard is recognized immediately.

Airway pressure and expired volume monitors with high/low alarms will detect most causes of breathing system or ventilator malfunction *providing the limits are reset at the beginning of each anaesthetic.* However, it is important to stress that the standard pressure disconnect alarm (usually set to provide an audible warning if a minimum pressure of 7.5 cm H_2O is not generated for 20 s) may fail to detect a significant leak or reduction in fresh gas flow because a combination of a high flow from the ventilator and a high resistance in the ventilator tubing distal to the alarm may generate enough pressure in the system to satisfy the low pressure limit. Furthermore, the high pressure alarm on such a device may be set at a level which exceeds the blow-off valve pressure in the breathing system or ventilator, so that the alarm ceases to function as intended. There is thus no substitute for both pressure and expired volume monitoring when assessing ventilator function.

PATIENT MONITORING

The first essential is that both ventilation and circulation should be monitored continuously, alarms being required if the anaesthetist is likely to be distracted from this task for more than 30 s. It is usually reasonable to rely on the observation of chest wall movement and the excursion of the reservoir bag during spontaneous breathing or manually-controlled ventilation. However, during mechanically-controlled ventilation it is essential to monitor both airway pressure and expired volume, high/low alarms again being required if the anaesthetist cannot observe these monitors continuously.

The circulation presents a greater problem because it is difficult to palpate the pulse continuously for long periods. Auscultation of the heart sounds by precordial or oesophageal stethoscope is a valuable alternative, particularly in neonatal anaesthesia when arterial pressure monitoring is more difficult. Unfortunately, the prolonged use of a binaural stethoscope may be limited by discomfort, whilst repeated use of a fitted monaural earpiece may lead to otitis externa in susceptible individuals. For these reasons many anaesthetists rely on the finger plethysmogram to provide a guide to the adequacy of the central and peripheral circulation. The most satisfactory device is one which provides an analogue signal of the pulse wave, since it enables changes in amplitude and waveform to be detected. Pulse meters which do not provide such a display should be treated with suspicion; one device recently tested produced a steady reading of 80 beat min^{-1} when the probe was wrapped round a pencil.

The use of the ECG is now widespread and in many hospitals it is routinely applied to every patient. However, it is well known that normal ECG activity may be present even though no pulse is palpable. The main use of the ECG should, therefore, be to detect changes in heart rate and to diagnose arrhythmias or other signs of abnormal electrical activity which might indicate myocardial ischaemia. The therapy of arrhythmias should be based on both the nature of the arrhythmia and its effect on cardiac output.

Although methods for the continuous indirect measurement of arterial pressure are now becoming commercially available, these are still at an early stage of development. Most discontinuous methods in current use are subject to error, and there is little evidence that any of the new automated devices are any more accurate than traditional methods (Johnson and Kerr, 1985). However, the automated arterial pressure monitors can perform repeated measurements whilst the anaesthetist is concentrating on other tasks and so may improve the continuity and thus the overall quality of monitoring.

The recent development of pulse oximeters, which both monitor the heart rate and provide a continuous measurement of arterial saturation, represents an enormous advance in monitoring (Taylor and Whitwam, 1986). These devices may be placed on the finger, ear lobe or nasal septum and differ from previous oximeters in that they are able to eliminate the background absorption attributable to tissue by measuring the light absorption at two different wavelengths at frequent intervals during each pulse. It is, therefore, possible to derive an absolute measure of oxygen saturation without precalibration. Pulse oximeters are sensitive to motion artefacts and may give inaccurate results when the pulse volume is reduced by blood loss or severe vasoconstriction. They may also be affected by the presence of excessive external illumination, bilirubin or extraneous dyes in the blood, or marked venous pulsations. Although some of the instruments automatically adjust the gain on the analogue display of pulse volume to ensure that the signal is clearly visible (and thereby destroy the amplitude information), the ability to provide a continuous display of both the heart rate and oxygen saturation is likely to make the use of such an instrument an essential requirement for every anaesthetic in the near future (New, 1985; Tytler and Seeley, 1986). It seems likely that the pulse oximeter will also become the standard instrument for monitoring oxygen saturation in neonates and children (Fait et al., 1985). Transcutaneous Po_2 measurement is useful in neonates, although it has a slower response than the pulse oximeter, is less accurate, and is greatly affected by changes in skin blood flow. It is of little value in adults (Barker and Tremper, 1985).

The use of end-tidal carbon dioxide monitoring is still controversial. The technique is in widespread use in the United States, mainly because it provides incontrovertible evidence that the tracheal tube is situated in the trachea, that carbon dioxide is being transported to the lungs and that it is being moved by ventilation to the site of sampling (Birmingham, Cheney and Ward, 1986). An increase in carbon dioxide concentration throughout inspiration will indicate that rebreathing is occurring but, as already mentioned, an inspired carbon dioxide concentration of zero at some point in the cycle does not guarantee that rebreathing is absent. An acute reduction in the end-tidal carbon dioxide concentration occurs when there is a sudden decrease in cardiac output or a large pulmonary embolus of air or blood clot. Although it has been claimed that the arterial to end-tidal Pco_2 difference is small during anaesthesia (Whitesell et al., 1981), there is other evidence which suggests that the use of end-tidal Pco_2 to predict arterial Pco_2 is too unreliable for clinical purposes. There are three sources of inaccuracy. First, many current analysers have a relatively slow response time and do not produce accurate end-tidal values at breathing frequencies greater than 15 b.p.m. This restricts their application in paediatric anaesthesia (Sasse, 1985). Second, the sampling site is critical and the loss of a sample volume of 500 ml min^{-1} may seriously affect the dynamics of paediatric or low flow, circle absorption breathing systems. Third, although the normal arterial to end-tidal carbon dioxide tension difference during anaesthesia is approximately 0.8 kPa (Nunn and Hill, 1960), this is markedly affected by inspired oxygen concentration (Larson and Severinghaus, 1962), tidal volume (Fletcher and Jonson, 1984), inspiratory: expiratory time ratio (Perez-Chada et al., 1983), hypotension or blood loss (Askrog, Pender and Eckenhoff, 1964) and lung disease (Takki, Aromaa and Kauste, 1972), and there appears to be marked variability with time as well as inter- and intra-patient variation. It has been reported that, even when the measurement is calibrated with a blood-gas measurement at the beginning of the anaesthetic, the mean error of subsequent estimates of arterial Pco_2 may be ±6 mm Hg (±0.9 kPa), whilst maximum errors may be as great as ±12 mm Hg (±1.8 kPa) (Raemer et al., 1983).

ESSENTIAL MONITORING

The foregoing discussion has indicated that all the monitors currently available have disadvantages which limit their usefulness. However, by integrating the use of a number of monitors, it is possible to minimize the number of occasions on which an abnormality is not detected.

TABLE I. *Essential (and desirable) machine-breathing system–ventilator monitors*

Monitor	Process monitored
Machine	
O_2 supply pressure failure alarm	Fresh gas oxygen supply
Fresh gas O_2 concentration	Fresh gas oxygen concentration
Flowmeters	Fresh gas composition and flow
(Fresh gas vapour analysis)	Fresh gas vapour concentration
Breathing system–ventilator	
Circle system inspired O_2 concentration	Fresh gas input; O_2/N_2O uptake, N_2 accumulation
Circle system inspired vapour concentration	Fresh gas input; vapour delivery/uptake
Expired volume	Breathing system–patient leaks Tidal or minute ventilation
End-tidal CO_2	CO_2 transport to sampling site Alveolar ventilation/CO_2 production Rebreathing (controlled ventilation)
Expired volume plus end-tidal CO_2	Rebreathing (spontaneous ventilation)
Airway pressure	Expiratory valve function Ventilator function Total thoracic compliance and airway resistance

Anaesthetic machine, breathing systems and ventilator

There can be no doubt that every anaesthetic machine should be fitted with an oxygen pressure failure warning device and a fresh gas oxygen concentration monitor with high/low alarms. An inspired oxygen monitor should be used when a circle system is selected in order to guard against the risk of hypoxia as a result of a reduction in fresh gas flow into the breathing system, a difference in oxygen and nitrous oxide uptake or the accumulation of nitrogen when low fresh gas flows are being used. Tidal volume may be estimated from the excursion of the reservoir bag during spontaneous ventilation with any breathing system, but an expired volume meter (situated at the patient connection port with Mapleson A and D systems) should always be used during controlled mechanical ventilation. An end-tidal carbon dioxide monitor is highly desirable to indicate first, that carbon dioxide is being transferred from the tissues to the breathing system and second, that rebreathing of carbon dioxide is not occurring. A high airway pressure alarm is also essential (table I).

Patient monitoring

It is useful to categorize operations as minor, standard or major (table II).

A *minor operation* may be defined as a procedure lasting less than 30 min, during which an inhalation anaesthetic is administered by face mask. The first essential is some device which provides a continuous indication that a pulse is present. This may be a finger on the pulse, a precordial or oesophageal stethoscope, or a finger plethysmogram. This should be supplemented by an ECG and indirect arterial pressure measurement. A pulse oximeter is highly desirable. The addition of an expired volume monitor between breathing system and facepiece is of doubtful value. It increases deadspace and the movement of the reservoir bag provides a good guide to ventilation and leaks from the system.

A *standard operation* would include most routine operations in relatively healthy patients in whom a tracheal tube is used. The operations would usually last less than 3 h and blood loss would be less than 10% of the predicted blood volume. The essential monitoring is as above. If controlled mechanical ventilation is used, expired volume

TABLE II. *Essential (and desirable) patient monitoring (in addition to that incorporated in the breathing system and ventilator). Operations defined as in text*

Essential	Desirable
Minor operation	
Continuous pulse monitor—finger plethysmograph, or precordial or oesophageal stethoscope	
ECG	
Indirect arterial pressure	Pulse oximeter
Standard operation	
As above	Temperature
	Neuromuscular blockade
Major operation	
ECG	Neuromuscular blockade
Pulse oximeter	
Arterial pressure (direct)	
Central venous pressure (direct)	
Blood loss measurement	
Urine output	
Temperature:	
Patient	
Bloodwarmer, mattress	
Inspired gas	
Blood-gas analysis, K^+ concn	
Clotting tests	

measuring is essential and end-tidal carbon dioxide monitoring highly desirable. Continuous monitoring of neuromuscular blockade is highly desirable if there is a possibility of an abnormal response to blocking agents if repeated doses are used or if a drug with a rapid termination of action (such as atracurium) is being used. Temperature monitoring is desirable if the abdominal contents are exposed or the theatre temperature is not controlled.

A *major operation* may be defined by a duration of operation greater than 3 h, expected blood loss greater than 10%, or surgery involving the lungs, central nervous system or cardiovascular system. The monitoring should be as above, but one would consider direct arterial and central venous pressure measurement and blood-gas analysis in the majority of patients. The need for neuromuscular blockade monitoring increases with the duration and severity of the operation unless postoperative ventilatory support is planned. Heat conservation with a water blanket and blood warmer is important, and both the temperature of the patient and the temperature of these devices should be measured continuously. As the duration of surgery increases, there is a greater need for humidification of inspired gas. If hot-water humidifiers are used, it is necessary to monitor inspired gas temperature for safety and as an index of humidity. Renal function should be assessed by the continuous measurement of urine output. When transfusion is large, or there are problems with haemostasis, blood clotting must be assessed. In specific circumstances extra monitors may be required (e.g. ultrasound for detection of air embolus in neurosurgery, a Swan–Ganz catheter if left ventricular filling pressure is likely to be abnormal, blood sugar and potassium concentration measurement in diabetics, and haematocrit estimations in patients with burns, etc.).

There are special problems in monitoring neonates (Ward, 1985) because of the small size, delicate skin and rapid changes in physiological state. It is often better to rely on one device such as an oesophageal stethoscope or precordial stethoscope, providing that monitoring is continuous. For most operations, the monitoring of ECG is quite practicable, but faster sweep rates are required to cope with the faster heart rates. Pulse oximetry appears to be a most useful monitor in critically ill children (Fait et al., 1985), and is less affected by circulatory changes than is transcutaneous $P\text{o}_2$. Most clinically available gas and vapour analysers have response times inadequate to provide useful measurements in the presence of fast rates of ventilation (Sasse, 1985). Temperature monitoring is essential in all but the shortest operations.

All the above basic requirements must be modified to take account of the patient's preoperative condition and of any possible changes in physiology induced by surgery. For example, auscultation of the breath sounds via an oesphogeal stethoscope, or observation of the airway pressure with a constant flow generator type of ventilator can provide a most useful guide to the degree of bronchospasm present in a patient with acute or chronic airways obstruction, whilst direct monitoring of aortic pressure may be required in patients immediately after cardiopulmonary bypass to overcome the problems of inaccurate readings from the radial artery as a result of severe arterial spasm.

CONCLUSION

Monitoring apparatus is steadily becoming more reliable and we are now able to make continuous measurements of essential variables, such as arterial and venous pressure and arterial oxygen saturation. We should, therefore, be moving towards the use of fewer but more reliable monitoring devices and we should ensure that this monitoring is continued until recovery is complete. Because of the limitations of the individual monitors outlined above, it is necessary to use a combination of monitoring devices which is capable of detecting the majority of hazard situations. Machine monitors should be carefully related to the design of the machine and to the breathing system used, should be calibrated and switched on automatically when the machine is brought into use, and should, whenever possible, check each other. Monitoring should be specific for the variable to be measured—for example one should not use a pressure alarm to monitor airway leak, and each monitor should have a clearly visible display with appropriate alarm sounds. The display should be in the form of an integrated system which indicates the priority of alarms in such a way that the anaesthetist can differentiate minor malfunction from an emergency which requires immediate attention.

There are still some situations in which it is safer to use a single monitor such as an oesophageal stethoscope rather than a vast array of more complicated devices. Furthermore, there is no direct evidence that the provision of the monitors discussed above will significantly improve morbidity or mortality during anaesthesia. However, those who have used patient monitors extensively will often have experienced situations in which a monitor has enabled a potentially undesirable outcome to be avoided. Since a serious complication may occur as easily during a minor surgical procedure as during a major operation, it is essential that the appropriate monitoring should be applied routinely to all patients undergoing surgery. Shortage of funds in the N.H.S. is no excuse. The capital cost of using the monitors recommended above for the standard operation (assuming a use on 2000 patients a year for a minimum of 5 years) is less than £2.00 per patient—much less than the cost of a few sutures used during the operation, and a small price to pay for patient safety.

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SAFER DESIGN OF ANAESTHETIC EQUIPMENT

P. W. THOMPSON

"*Doubtless God could have made a better berry (strawberry), but doubtless God never did*".
(Butler, W. in Walton, I. *The Compleat Angler*, Part I, Chapter 5.)

Many anaesthetists might fairly feel that the anaesthetic machine of today has reached a degree of satisfactory performance which makes it totally acceptable and take a view that further sophistication and refinement would not justify the further research and development input required, to say nothing of the financial implications. There are many books on the history of anaesthesia which incorporate information on the development of anaesthetic machines, a subject which has recently been reviewed by Thompson and Wilkinson in this Journal (1985).

Accumulated literature on anaesthetic apparatus hazards is even more abundant and it is, indeed, unusual for any issue of an anaesthetic journal not to include some report, however brief, of yet another equipment incident. However, vast as the accumulation of this literature now is, there are, fortunately, relatively few such incidents which have resulted in death or permanent damage to patients. In their report on anaesthetic mortality Lunn and Mushin (1982), analysing 6060 deaths within 6 days of operation, identified a group of 58 deaths "for which the assessors believed anaesthesia was *totally* responsible". Examples of events quoted by assessors in this group listed one failure of a defibrillator and one failure of a ventilator as equipment faults to which death could be attributed. However, they considered that inadequate provision of essential monitoring instruments was a factor which could not be ignored and they were critical of failure to use such facilities when they were available.

It is not the purpose of this paper to review either the history of equipment development or the hazard literature yet again. Nevertheless, as long as the anaesthetic apparatus itself is the centrepiece, it cannot be discussed without also looking at the role of the user *vis-à-vis* safety, the place of monitoring, the maintenance of equipment, and standardization.

The Role of the User

Looking more closely at the role of the anaesthetist in connection with equipment accidents, the conclusions of some writers cannot be ignored. Craig and Wilson (1981) collected reports of anaesthetic misadventures from a District General Hospital and analysed 81 of these. They concluded that human error was more frequently responsible than equipment failure and that failure to perform a normal check of anaesthetic apparatus was the most frequently associated factor. Cooper and colleagues (1978), analysing "preventable anaesthesia mishaps" examined 359 incidents. Equipment failure was involved in 40% and, of these, 12% (six incidents) were associated with functional failure of anaesthetic machines, not including the breathing system—a figure which may suggest a high degree of reliability and effective maintenance. They pointed out "on the other hand it is conceivable that anaesthesia machines may be failing in ways that are not easily or rapidly detected by most anaesthetists". Throughout the literature it is argued that no equipment of any type can basically be better or safer than the person using it. For example, while it is generally recognized that the automatic pilot on modern aeroplanes is less liable to judgmental errors than human pilots, there is still a margin of error in that they require the accurate insertion of appropriate data in the first place. The incorrect input of, for example, wind speed, or the misinterpretation of some information in a flight plan, can result in a major disaster. Sophisticated as such equipment now is, the published figures on flying accidents internationally still place human error as a major contributory factor. Indeed, work in fields of safety investigation, such as rail or flying accidents, or mountain climbing, could well be

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applied to the specialty of anaesthesia. The contributors to *Pilot Error* (Hurst, 1977) and *Pilot Error: Human Factors* (Hurst and Hurst, 1982) emphasize repeatedly points which are of fundamental importance to safety in anaesthesia. To give just three examples: "Too many pilots let themselves be carried away by an emergency to such an extent that solving the emergency takes priority over flying the aircraft"; "Man can only, in fact, attend to one thing at a time"; and "Individuals may deal with pieces of information quickly and badly or may concentrate entirely on one source of information to the exclusion of all others. They may confuse information obtained from two or more sources or may even seek to escape from the situation by ignoring all the inputs, possibly by indulging in a totally irrelevant activity". The importance of the user cannot be more succinctly expressed than it was by Schreiber (1985) writing in the U.S.A.: "It is, therefore, absolutely necessary that an anaesthesia system be operated under the constant surveillance of a trained operator and it must be understood that the anaesthesia system cannot be designed to automatically respond to a change in a patient's condition or to an operator error".

Pre-use check of equipment

Before using any equipment it behoves the user to satisfy himself of its fitness for the purpose in mind and of his understanding of its correct operation. It is appropriate, therefore, to give some consideration to the role of the anaesthetist in checking his anaesthetic equipment. The place of the check list in the anaesthetist's code of practice has been discussed by Cundy and Baldock (1982) and Heath (1983). Lunn and Mushin (1982) reported that, in 17.8% of the cases they considered, the anaesthetic machine was not tested before use.

A variety of procedural drills has been produced, some published in books or journals or in manufacturers' manuals, others limited to their author's own hospital. There is really nothing new in suggesting that the anaesthetist should check his equipment. From the earliest days such simple measures as "a quick sniff to make sure that the ether was not chloroform" was a regular part of practice. However, increasing awareness of apparatus problems and pipeline accidents, some of them major, has highlighted the importance of the "cock-pit drill". The subject has been well reviewed recently by Ward (1985). Once again it must be stressed that any safety check is dependent on the careful implementation of it by the user. The writer has repeatedly warned "Do not adjust your mind, there is a fault in reality". It is all too easy to see what it is expected to see and to overlook an obvious error. Particular attention may be drawn to the simply expressed "Protocol for checking an anaesthetic machine before use" issued in 1980 by the Faculty of Anaesthetists of the Royal Australasian College of Surgeons (Protocol, 1980). Rapid reminders were listed as (1) gases, (2) rotameters, (3) vaporizers, (4) pre-circuit leaks, (5) breathing system selection, (6) circle system. Whatever procedure is adopted, it is essential that it is followed meticulously. A superficial slapdash check is no better, and could even be worse, than no check at all.

Present developments

The main thrust of design development at present seems to be aimed at increased safety, which is to be achieved by greater accuracy of controls (particularly important when low flow breathing systems are to be used) and increased information about what is being given to the patient, and the condition of the patient.

Incorporation of Monitoring and Safety Devices

Although monitoring is the subject of a separate paper in this issue, it is impossible to consider the safer design of anaesthetic equipment without referring to it. Over the years a wide range of views has been expressed as to the value of monitoring equipment. At the one extreme there is the view that a finger on the pulse will tell all, while at the other end Schreiber (1985) and Schreiber and Schreiber (1986) have reviewed the subject and the value of such equipment in considerable detail.

There are some who consider that the ingenuity and resourcefulness devoted to the elimination of equipment hazards may be misdirected in concentrating on the development of warning and safety devices. This philosophy was stressed by Bruner (1984), who felt compelled to go so far as to say "I would specifically indict safety developments and regulation on three grounds. First, proposed safety devices add to the complexity of apparatus; Second, what is the rationale for insisting upon the utilisation of a putative safety device that has a higher probability of failure (in the 'no alarm' mode) than the occurrence of the event that the safety device is supposed to detect? Third...the

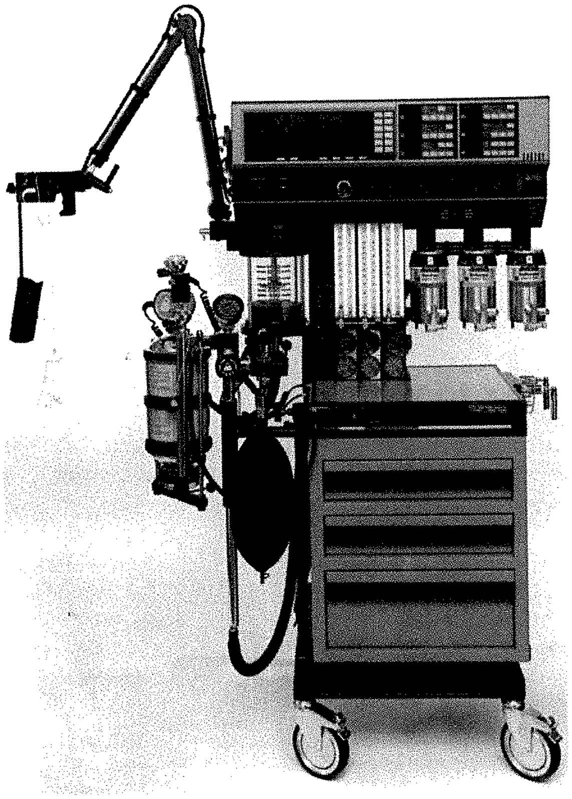


FIG. 1. The Dräger Narkomed 3 anaesthetic machine. (Courtesy of North American Dräger.)

present tenor of the crusade in regard to safety is diversionary not only of money and time but also of attention... the screen of the ECG monitor is the wrong place to look for trouble!"

This view would probably not receive widespread agreement in today's medico–legal climate, and the importance of adequate monitoring is being increasingly recognized. For example, Schreiber (1985) correlated the possible causes of hypoxia during anaesthesia against safety devices and other indicators. He attempted to establish a rating of the importance of the various safety devices and indicators and stressed that it is essential that all devices and indicators are scanned periodically. In his tabular analysis correlating hypoxia causes against safety devices and other indicators (which did not include the carbon dioxide monitor), he concluded that the oxygen analyser had the greatest potential for alerting the anaesthetist to hypoxic situations. He was in no doubt that "the use of an oxygen analyser with any anesthesia breathing system is essential since the reliability of oxygen sensors has become acceptable" and that "the use of an oxygen analyser with an anesthesia system is the single most important measure to prevent hypoxia". In further correlation of causes of apnoea against safety devices and other indicators (Schreiber, 1985), he showed that the ventilatory flowmeter and the carbon dioxide monitor rated most highly. He discussed in detail the importance of the anaesthetist being aware of the safety limitations of such devices and pointed out that the siting of the oxygen sensor was important. For example, monitoring the oxygen concentration in the fresh gas flow downstream of the common gas outlet of the anaesthetic machine could represent only a limited safety potential with some modified breathing systems such as the coaxial.

Another method of tackling this problem favoured by Schreiber is the "oxygen ratio monitor". This device activates an alarm if the percentage of oxygen concentration in the mixture of oxygen and nitrous oxide decreases to less than a certain predetermined value. A further development of this device is the oxygen ratio monitor controller (ORMC), the function of which is similar, but which has the additional capability to control the nitrous oxide flow in order to maintain a safe percentage of oxygen in an oxygen–nitrous oxide mixture.

Schreiber's philosophy has been the guiding factor in the development of the latest range of anaesthetic equipment produced by the North America Dräger Company, the Narkomed 3 System. This apparatus (fig. 1) aims to eliminate the array of stand-alone monitors by building them into the anaesthetic machine. Six integrated monitors, based on a data network, are available, from a total of eight, for display of patient-status data. The eight options are: oxygen concentration, pulse oximetry, ventilatory volumes, anaesthetic concentrations, breathing pressures, carbon dioxide, arterial pressures and temperatures.

A comparable philosophy has been developed in the U.K. by Sykes and Sugg, of the Nuffield Department of Anaesthetics, Oxford, and Penlon Limited, respectively, on the basic premise that, ideally, all functions of an anaesthetic machine would be monitored continuously. Since this can only be done really effectively by electronic control, they have incorporated this approach in their Penstar apparatus (fig. 2). Even a cursory glance at their fresh gas and vaporizer circuit (fig.

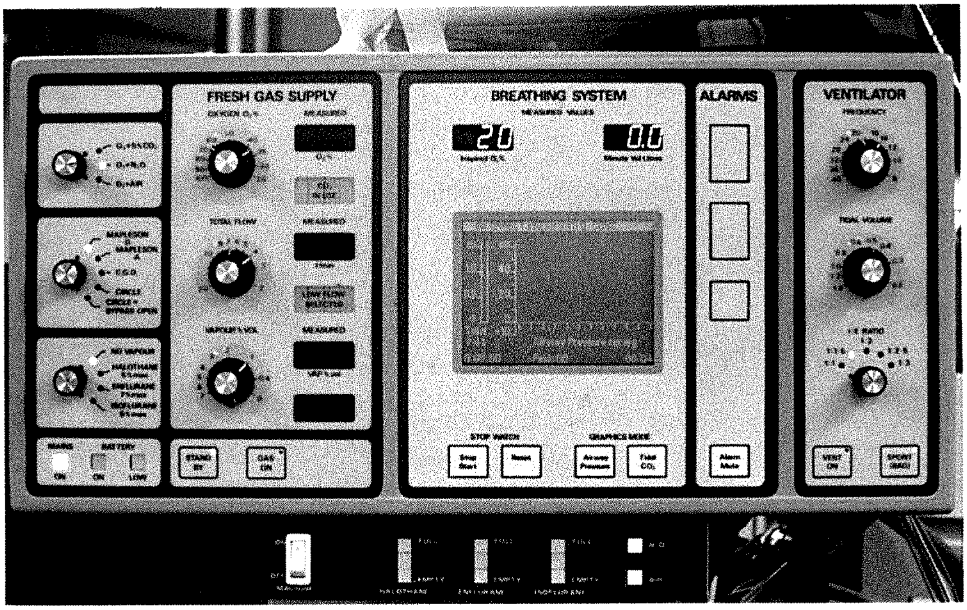


FIG. 2. The Penlon "Penstar" anaesthetic machine. (Courtesy of Penlon Limited.)

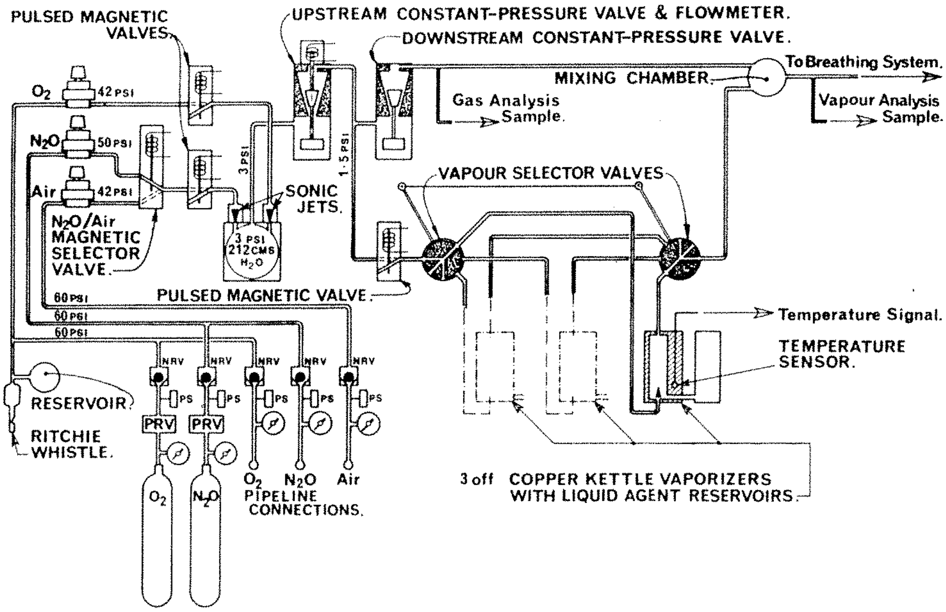


FIG. 3. The fresh gas and vaporizer system of the Penlon "Penstar" anaesthetic machine. (Courtesy of Penlon Limited.)

3) and one of their breathing systems diagrams (fig. 4) will make clear the degree of sophistication which is called for by this approach. Gas flows, for example, are pulsed electronically in 10-ml quanta and anaesthetic vapours are treated similarly. A centralized alarm panel allows the display of up to eight warnings (fig. 5).

A third apparatus which illustrates the new approach is the "Ohmeda Excel Series" (fig. 6). The stress is again on safety, and the main features listed by the makers are:

(1) Flowmeter safety link 25. This is a physical chain link between the oxygen and nitrous oxide flow control valves which operates so as to

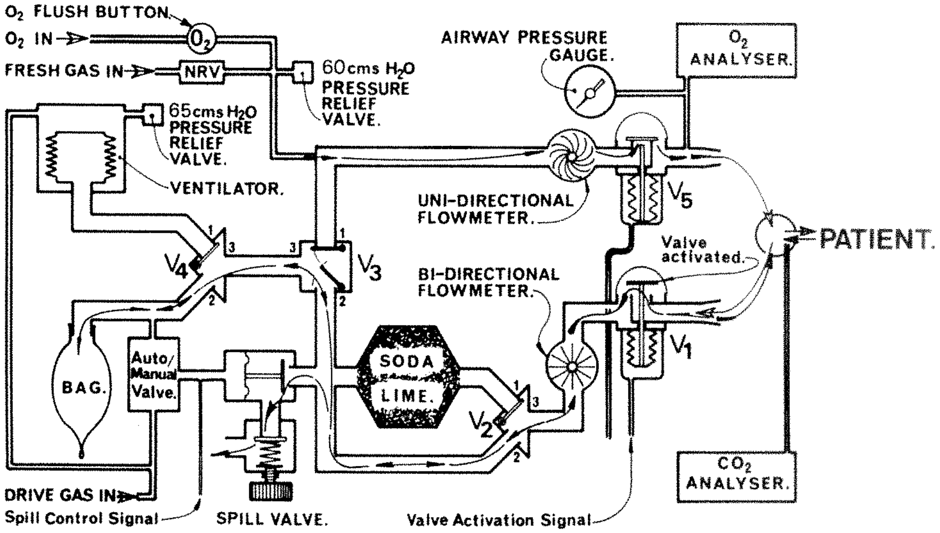
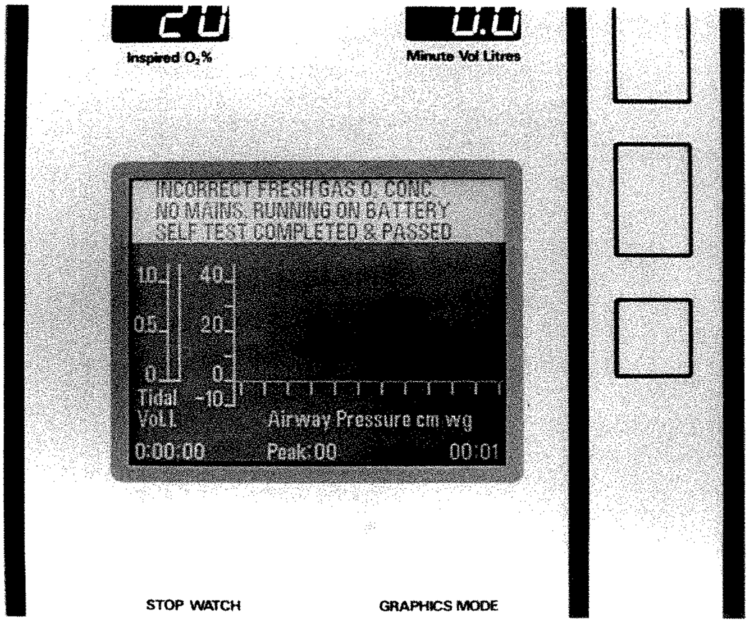


FIG. 4. The Mapleson D breathing system of the Penlon "Penstar" anaesthetic machine. (Courtesy of Penlon Limited.)



INCORRECT FRESH GAS O_2 CONC
NO MAINS. RUNNING ON BATTERY
SELF TEST COMPLETED & PASSED

FIG. 5. The display panel of the Penlon "Penstar" anaesthetic machine. (Courtesy of Penlon Limited.)

maintain, at all times, a minimum of 25% (nominal, subject to a tolerance of ±4%) oxygen in oxygen–nitrous oxide mixtures.

(2) Preferential oxygen. Ensures that oxygen is the last gas to enter the mixed gas flow to the patient (ISO5358, 1980).

(3) Oxygen failure warning system. Provides an audible warning when oxygen supply pressure fails and shuts off the remaining gas flow. The patient can breathe room air through the machine if able to do so.

(4) Carbon dioxide flow limitation. Normal carbon dioxide flow valves allow up to 15–20 litre min^{-1} to flow through the system when fully opened. Accidents have occurred because of this feature. In this apparatus, a physical restriction prevents a flow greater than 2.0 litre min^{-1}.

(5) Pin-indexed flowmeter tube blocks. Means

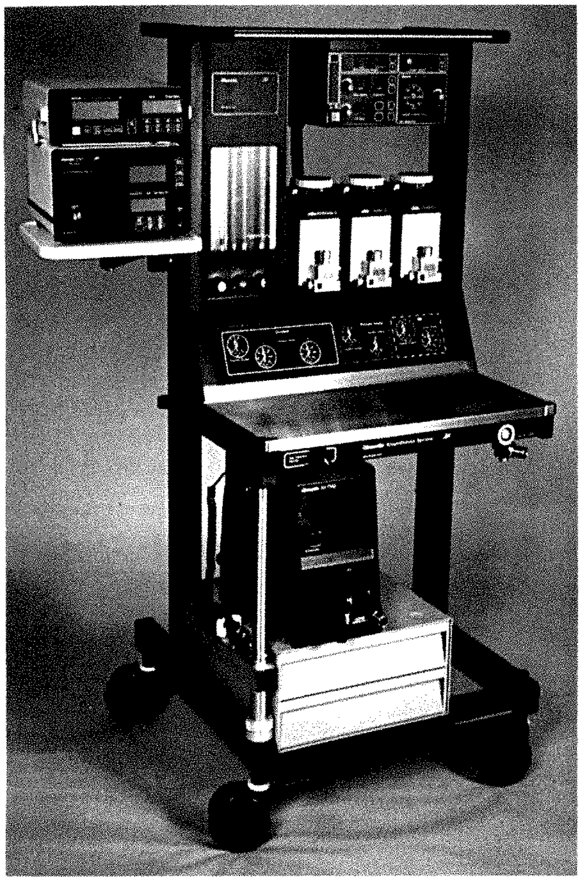


FIG. 6. The Ohmeda Excel Series anaesthetic machine. (Courtesy of Ohmeda.)

that it is impossible to transpose flow tubes during servicing or repair.

(6) Selectatec Tec 4 vaporizer system. Features a physical interlock which allows only one vaporizer (and hence one agent) to be used at any one time. A unique gas flow channelling system also prevents the uptake of even minute amounts of a second agent if one is mounted on the machine.

(7) Non-interchangeable internal pipework connections.

(8) Stringent leak test procedures.

(9) Integrated electronic ventilator (OAV 7700S) which contains multiple alarms for the following:

(a) Disconnect (both pressure and expired minute volume based alarms). This alarm system will pick up small leaks in the patient breathing system.

(b) Over pressure. Alarms and cycles the ventilator into the expiratory phase at an operator-set pressure threshold.

(c) Gas and electric failure.

(d) Oxygen concentration. The integrated ventilator contains an inbuilt oxygen concentration monitor and alarms (audible and visual).

(e) Patient cable management. Patient cables are ducted through the machine to the patient to remove visual obstruction (other cable management systems similarly manage patient cables from other monitors placed on the monitor shelves).

Another approach to the prevention of hypoxic mixtures is the development of the blender. Several anaesthetic machines such as the Quantiflex now incorporate mixers which are so constructed that it is impossible to give less than, say, 30% oxygen in the inspired mixture. However, there will certainly be debates as to the level at which the minimum should be set. For example, some might say that they would wish to go as low as 18% oxygen while some would still desire to be able to give pure nitrous oxide. This raises the possibility of incorporating bypasses or mutes for safety devices and arguments as to whether such bypasses or mutes should be banned in relevant equipment standards. A middle course would be the provision in such equipment of maximum time delays.

Cost of equipment

The brief descriptions of three new anaesthetic machines given above might well raise an immediate query in the reader's mind, "Surely the cost is prohibitive, isn't it?" No effective answer can be given to this, since it is quite impossible ever to quantify the price of increased safety. However, it should be pointed out that the machine with incorporated monitoring devices is unlikely to be more expensive than a simpler version with added stand-alone equipment which may, coincidentally, be more liable to accidental damage.

Modifications of equipment

Cooper and colleagues (1978) drew attention to the dangers which may arise from local modifications of anaesthetic equipment. They cited an example where all anaesthetic machines in one hospital were modified by replacement of the oxygen flow control knob with a large custom-made knob designed to provide obvious distinction by touch from the nitrous oxide knob. Eight incidents were reported in which the oxygen flow was inadvertently decreased, the cause being movement of this special knob by impact from an object placed on the machine's surface.

Recently, the author left an anaesthetized dental patient in the care of a trainee. The patient was breathing spontaneously through a nasotracheal tube with a scavenging valve connected to the catheter mount in a Magill, Mapleson A system. Two lengths of corrugated breathing tube were in use. Some 10 min later the author was called urgently because the patient was waking up and the ECG showed serious abnormalities. The cause was detected at once—the trainee had moved the scavenging valve from its original position back to the reservoir bag in the mistaken belief that he was using a Bain's system! Fortunately no harm was done, but the incident serves only too well to emphasize the necessity for anyone, at any level of experience, using any form of anaesthetic apparatus, to have a clear understanding of the equipment and to appreciate the importance of refraining from making unauthorized modifications.

Maintenance

The importance of maintenance cannot be overemphasized and manufacturers of equipment are strongly recommended, and indeed, by some published International or British Standards, required, to state in their accompanying literature the maintenance procedures and service intervals which they recommend. Such maintenance is normally carried out under contract with the manufacturer or an associate or by in-house maintenance. Many manufacturers are prepared to give factory training to in-house technicians insofar as their own equipment is concerned and to provide supplies of appropriate spare parts.

Whoever or however such maintenance is carried out, it is essential that full checks are performed at the end of the procedure and that clear notices are displayed on the machine that it has been serviced, so that the first user may satisfy him/herself as to its performance and also be alerted should any untoward or unexplained incident occur during use.

Ward (1985) discussed some of the problems of equipment maintenance and drew attention to the danger of sending equipment to the hospital engineers who "are often ignorant of the principles involved in anaesthetic equipment". Their well-meaning assistance or interference has, only too often, led to accidents resulting from inappropriate repairs or alterations. It is not unusual for the Safety Committee of the Association of Anaesthetists to be informed of post-maintenance faults or to hear of hazards arising from screws etc., which had been inserted by "Mr Nobody". Bearing in mind that this is so, the extreme danger of referring equipment to unsuitable engineers or attempting do-it-yourself maintenance cannot be over emphasized.

Finally, it must not be forgotten that previously safe anaesthetic apparatus may be rendered highly dangerous by errors during servicing and maintenance (DHSS, 1982; Bonsu and Stead, 1983; Judkins and Sage, 1983). At the time of writing there is no universally agreed code of practice for ensuring that first users of serviced equipment are made fully aware that they are the first. However, it is anticipated that, in the U.K., agreement will be reached in the near future between the interested parties about this problem. The whole subject of management of equipment is discussed fully in *Health Equipment Information* No. 98 (Jan 1982), which was reprinted with amendments in 1984 as *Health Equipment Information* No. 176 (October 1984).

Standardization of anaesthetic equipment

In 1931 Hadfield, writing on "Chloroform by the open method" commented: "unfortunately the bore of the lead tops of the bottles differs, and consequently the size of a drop is variable. It is to be regretted that no maker has taken the trouble to issue a drop-bottle with holes in standard sizes like the jets on a motor carburettor". Over the past few years considerable advances have been made in the development of standards for anaesthetic equipment, and the history of this work was reported on by Hillard (1968), Thompson (1983, 1984) and Greenbaum (1985). A considerable number of International and British Standards have now appeared and, while progress is slow, some real advances have been made. ISO 5358 (1980) deals with "Continuous flow inhalational anaesthetic apparatus (anaesthetic machines) for use with humans" under the following headings: Medical gas cylinder connections, Pipeline inlet connections, Pressure gauges and cylinder contents indicators, Pressure regulators, Machine gas piping, Flow control valves, Flowmeters, Connections for vaporizers, Mixing devices, Flowmeter-controlled vaporizer systems, Concentration-calibrated vaporizers, Non-calibrated vaporizers, Common gas outlet of the machine, Gas power outlets, Oxygen flush valves, and Oxygen supply failure precautions.

The importance of this work can hardly be over

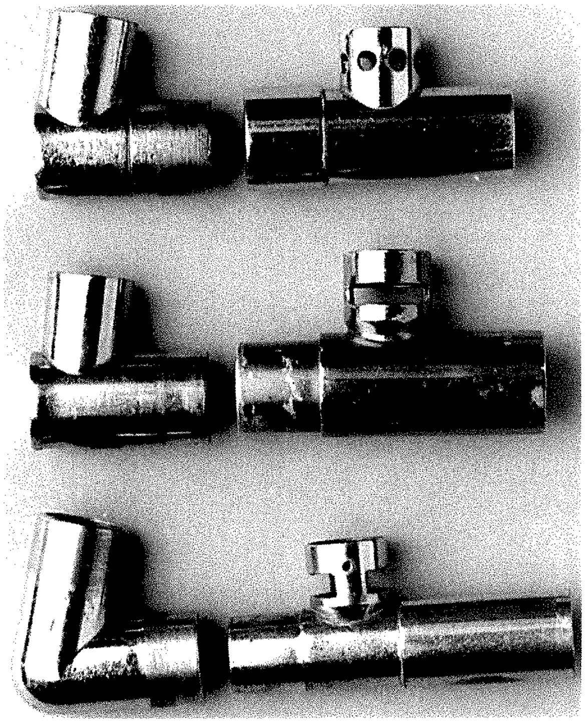


FIG. 7. Non-fitting (incompatible) expiratory valve units and angle-pieces.

emphasized. Figure 7 illustrates a simple situation which was all too common a few years ago, when one could find on an anaesthetic machine three angle-pieces and three expiratory valve units, not one of which would mate with any other. The current U.K. practice of anaesthetizing patients in an anaesthetic room using one apparatus and then transferring to a second one waiting in the operating theatre can still result in sudden connection probems. Only recently the author was, to his great amazement, confronted with a 22-mm McKesson expiratory valve assembly on the second machine, and this in a 10-theatre suite in a new hospital which so far as anyone knew had never had such an item at any time!

One fundamental aim of standardization has always been an increase in patient safety. To a considerable extent this may depend on the interchangeability of apparatus made by different manufacturers. Certainly, there lies herein increased safety in that the anaesthetist is less likely at a moment of crisis to find himself unable to connect one part of a breathing system to another. However, while most such components can now be fitted together, there is still much to be done in ensuring that they remain fitted together (Shaw, Davis and Anderson, 1982; Spurring and Small, 1983; Harrison, Tomlinson and Mann, 1984; Heath, 1984; Keddie, 1984). The Little Report (Little, 1983) examined the whole problem of disconnection within breathing systems in great detail and strongly recommended the use of locking connectors at all joints. The Final Report of the U.S. Food and Drug Administration (1986) is now published. The call for locking connectors would seem to be gaining favour generally, but some of the designs produced so far have not always been received as satisfactory.

CONCLUSION

An attempt has been made to indicate the lines along which designers seem to be thinking. It is stressed yet again that, whatever contributions to safety are made by design improvements, their effect in practice still depends on their understanding and implementation by the user, reliable and regular maintenance, the avoidance of local modifications and the development, as rapidly as possible, of effective National and International Standards for equipment.

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The author is deeply indebted to Peter Schreiber for permission to draw quite heavily on his published work, and to Mrs C. Ellis for the tact, patience and skill which she has shown during the preparation of the manuscript.

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EDUCATION IN ANAESTHETIC SAFETY

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While anaesthesia may appear to be an inherently dangerous process, it has a remarkably good safety record. Indeed, if the mortality attributable to anaesthesia was anything but small, it is doubtful if the administration of dangerous vapours would ever have gained acceptance, even in the last century. With its remarkable safety record and because few patients appear for anaesthesia alone, but always to allow some other therapeutic or diagnostic procedure, such deaths as do occur have always attracted considerable attention. When such untoward events are examined, it is customary for them to be described—in retrospect—as avoidable or as being associated with sub-standard care. Keats (1979) has taken a slightly different approach in emphasizing that any application of a drug or technique will almost certainly have an associated risk, and that such risks may lead to untoward events. Thus, whilst it is easy in looking back at events to see patterns that may lead to disaster, it is not so easy at the time when the events occur. Somewhat later, Keats re-emphasized the importance of a cost–benefit approach to safety studies and also the need for better quality information (Keats, 1983).

This essay is based on the hypothesis that more attention to education in safety should lead to an improved standard of care. In suggesting lines of approach, it is necessary first to survey the common types of anaesthetic accident, subsequently to examine the psychological factors in decisions attributable to human error and, finally, to suggest some strategies that might lead to a reduction in anaesthetic morbidity and mortality.

ANAESTHETIC MORBIDITY AND MORTALITY

In the 19th century, mortality resulting from anaesthesia with chloroform, administered usually by an open-drop method, was probably of the order 1:2000 administrations (Sykes, 1961). Accepting that the nature and extent of surgery has changed out of all recognition since then, and that many more elderly patients with grossly abnormal physiology are now anaesthetized, current estimates of deaths from anaesthesia are in the region of 1:8000 (Harrison, 1985). Caesarean section is well recognized to pose specific anaesthetic hazards. The latest Confidential Enquiry into Maternal Mortality in England and Wales suggested that anaesthetic mortality was of the order 1:8821 for the years 1979–82, compared with 1:5437 for the years 1970–72 (Turnbull et al., 1986). With such a low incidence it becomes almost impossible to demonstrate statistically that any one change in drug use or in technique is leading to an improvement.

Nevertheless, examination of reports such as those into maternal mortality reveals the commoner patterns associated with anaesthetic disaster. The list of events is depressingly familiar (table I) and suggests that human factors are usually the indirect cause. (It might be noted that the only cause listed in the first report (Walker et al., 1957) that is missing from the later ones, is death following the administration of chloroform!) Harrison (1985) gives a similar list of causes of anaesthetic-associated deaths for his surveys in Groote-Schurr—problems with: tracheal tubes, neuromuscular blocking drugs, inadequate postoperative supervision, vomiting and regurgitation, circulatory homeostasis, apparatus and human

TABLE I. *Events leading to maternal anaesthetic deaths 1979–81. (From Turnbull and colleagues (1986))*

Inhalation of stomach contents	8
With cricoid pressure	6
With Mg trisilicate	5
Difficulty with tracheal intubation	8
Misuse of drugs	2
Failure of postoperative care	7
Haemorrhage	4
Apparatus problems	2

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TABLE II. *Types of critical incident as percentages of total. (Data from Cooper, Newbower and Kitz (1984) in a survey of 1089 incidents)*

Equipment failure	13.4
Human error	68.2
Disconnections	13.0
Other	5.4

TABLE III. *Types of human error as percentages of total. (Data from Cooper, Newbower and Kitz (1984) in a survey of 583 reports)*

Wrong drug administered	24.0
Misuse of anaesthetic machine	22.0
Problem with airway management	16.0
Problem with breathing system	11.0
Fluid therapy mismanagement	5.0
I.v. infusion disconnection	6.0
Failure of monitoring	4.0
Other problems	12.0

performance. Surprisingly, entities such as halothane hepatitis and malignant hyperpyrexia do not feature in such lists.

Mortality surveys are useful in defining the major hazards of anaesthesia and, provided they also can give the denominator in the equation, the incidence of such events. Because most of these reports suggest that there may have been a lack of sufficient anaesthetic care, it is important to establish how often anaesthetists make mistakes and how often these lead to harm.

Cooper and his colleagues in Boston (Cooper et al., 1978; Cooper, Newbower and Kitz, 1984) endeavoured to address these problems, using a technique in which anaesthetists report, in confidence, *critical incidents* (the technique is described in detail elsewhere in this issue by Derrington and Smith (1987)). The 1984 report summarizes some 1089 incidents, of which 70 led to some patient harm. The types of incident are summarized in table II and it is clear that human error is by far the commonest cause. The types of error reported are shown in table III. Of the 583 "human errors" reported 111 (19%) involved a disconnection of a breathing system, an i.v. line or a monitoring device. It is important to note that there were 25 deaths reported in this series; that is to say, if a critical incident was noted (1089 occasions) the risk of it being followed by death was 1:43.6. Death may be rare, but critical incidents are much more common. If education can minimize these it should follow that the overall results will improve.

TABLE IV. *Associated factors producing critical incidents as percentages of total. (Data from Cooper, Newbower and Kitz, (1984) in a survey of 1089 incidents)*

Failures to check	9.5
First experience	8.9
Inadequate experience	8.6
Inattention/carelessness	7.1
Haste	5.6
Unfamiliarity	5.4
Visual restriction	3.5
Fatigue	2.3
Others	54.5

Cooper's group also were able to examine associated factors which contributed to the incident (table IV summarizes the more common ones). No one problem is outstanding, but all are familiar. Fatigue is often thought to be a common factor, but Cooper's evidence suggests that it contributes to only approximately 5% of critical incidents.

Williamson, Webb and Pryor (1985) have carried out a similar survey in Australia with similar results. They estimated that with some 9500 anaesthetics there were 114 critical incidents—a rate of 1:83 anaesthetics. There were no deaths in the series, but they were also able to identify factors that might prevent or reduce the numbers of such incidents. These included: continuous checking of the patient and the equipment, the better use of monitors, better experience and supervision and additional training.

HUMAN FACTORS IN ERRORS

The evidence presented so far has been selected to reveal the commoner patterns of anaesthetic mishap and the predisposing factors. It often appears that these mishaps are potentially avoidable, especially with the provision of better equipment, better training and supervision and improvements in monitoring. However, it is easy to ignore the human factors involved. Wylie (1975) entitled his lecture "There, but for the grace of God...." which recognizes that anaesthetics are given by humans and that all humans are liable to err. Allnutt (1982) has reviewed these factors in the context of aviation safety and a more general account of his work is given elsewhere in this issue (Allnutt, 1987). However, it is worth reiterating some of the factors which may lead astray the most diligent of individuals.

Information processing. Whilst our sensors are picking up a vast amount of information, it is probable that our short term memories can hold, at most, some seven separate items. Of these seven, we can act on only one at a time—and the other six are forgotten. Thus it may not be surprising that an anaesthetist concentrates exclusively on finding the entrance to the larynx and becomes oblivious to the passage of time, the development of cyanosis and, ultimately, cardiac arrest. The addition of pulse oximetry with the continuous display of arterial oxygen saturation will not help unless the associated warning of low saturation is made in such a way as to override the normal attention being paid to intubation. Even an assistant maintaining cricoid pressure may not realize that an alarm was sounding if his attention was on the airway.

Visual illusions. Whilst these are important in three-dimensional activities such as flying, it is possible to misinterpret such simple devices as the pressure gauge on a gas cylinder (Blum, 1971).

False hypotheses. It is all too easy to erect a false hypothesis that all is well when in fact it is not. Anyone who has a continuous recording of arterial pressure can compare that with his anaesthetic chart. The anaesthetic record will usually record pressures nearer those expected by the anaesthetist than those printed out automatically. We write down what we expect, not necessarily what happens! If our behaviour is derived from our expectation rather than from reality, then errors may occur.

Habit. In a stressful situation we are likely to rely on our ingrained habits to get us out of trouble. Provided that these are appropriate, all is well, but it becomes important to ensure that good habits are built in as early as possible in anaesthetic training.

Motivation. This can raise a number of problems in difficult circumstances. Whilst the delivery of safe anaesthesia is vital, there are other pressures on the anaesthetist, including the number of patients still awaiting surgery on an operating schedule, a desire to finish work at a reasonable time, or a desire to prove oneself by handling a difficult problem without calling for help. All these factors may affect our decisions.

Stress and the environment. These are difficult areas in which to provide accurate information, but it would seem obvious to note that factors such as sleep deprivation, absence of refreshment and the presence of drugs or alcohol can impair performance and affect safety. If airline pilots are expected to refrain from alcohol for several hours before flying, should not anaesthetists?

EDUCATION IN SAFETY

Most educational activities in anaesthesia are directed at producing effective anaesthesia. The learner is taught, by apprenticeship, by academic instruction and by his own reading and experience, techniques that lead to the desired result. What does not receive so much attention is a consideration of what may go wrong in anaesthesia, and how such events may be prevented, detected and treated. Often the activities of the anaesthetist are compared with those of a pilot, sadly with the limited comparison that the most dangerous times are at the start and the end of any anaesthetic or flight. What is of more use in the context of safety training is that, from the beginning, pilots are taught safety procedures. Thus a private pilot licensee will learn at his first lesson the importance of checking his machine and before attaining a licence will be familiar with the drills necessary to cope with the dangers of stalling, spinning or engine failure. Obviously, the pilot has a vital interest in acquiring these skills—his life depends on having them.

Beard and Hartley (1984) provide much useful advice in teaching and learning in higher education. They evaluate much of modern methods and in particular suggest that any training programme should include fairly detailed statements of its aims, goals and objectives. Thus one aim of anaesthetic training must be to improve safety. More specific goals need to be defined in terms of what part of safety is being considered, in how the aim is to be achieved and what methods are to be used. There should also be a method of checking that the required standard has been met.

The following paragraphs provide some ideas on what may be specific goals with some more detailed objectives. These are derived from the lists of the commoner accidents.

Airway problems

There are two common disasters. Either tracheal intubation is difficult, delayed or impossible, or else the tube is placed in the oesophagus. Both events may be complicated by the aspiration of vomit or regurgitated stomach contents. Three specific goals can be identified. The first is the difficult intubation, the second the oesophageal intubation and the third the problem of aspiration. The relevant objectives might be summarized:

Difficult intubation.

Preoperative assessment:
  Anatomy
  Pathology (especially pre-eclampsia)
  Previous anaesthetic record
Equipment necessary
Failed intubation drill (Tunstall, 1975)
  Abandon repeated attempts
  Maintain cricoid pressure
  Head-down and left-lateral position
  Oxygenate by IPPV
  Suction
  If obstructed, try release of cricoid pressure
  General anaesthesia by inhalation
  Abandon and use regional blockade

Oesophageal intubation.

Unless tracheal tube is seen to pass the cords, suspect oesophageal intubation.
If position of patient is changed, suspect that the tube may have become misplaced.
Check chest wall movement, auscultate the lung fields and the epigastrium. Realize that these may give false information.
Observe closely for the development of cyanosis or bradycardia.
Use a capnograph to detect carbon dioxide in the expired air.
If in any doubt at any stage, remove the tracheal tube.

Aspiration.

Assessment of patients at risk
Use of strategies to diminish risk
  Preoperative starvation
  Use of antacids
  Use of H_2-receptor blocking drugs
  Encouragement of gastric emptying
  Cricoid pressure (Sellick, 1961)
Management
  Suction
  Oxygen, IPPV, etc.
  Role of drugs such as diuretics, etc.

Such objectives and procedures require learning both in theory and in practice. The assessment of their effectiveness should be a function of the local teachers, but in any case will be a likely component of any professional examination.

It is also important to realize that safety strategies change over the years. For example, Sellick (1961) described the posture of the patient for his manoeuvre as "the patient lies supine with a slight head-down tilt. The head and neck are fully extended. This increases the anterior convexity of the cervical spine, stretches the oesophagus and prevents its lateral displacement....". Later he described cricoid pressure as being applied using one hand only of the assistant. Turnbull and his colleagues (1986) now describe the manoeuvre as needing both hands of the assistant, one to maintain cricoid pressure and one to maintain extension of the head at the atlanto-occipital joint.

Apparatus problems

Better use of anaesthetic apparatus should improve safety. The educational goals should encompass the following points:

Understanding. The increasing variety and complexity of modern equipment demands that none should be used without instruction in principles of working of any equipment, in its practical use and in the ways in which its performance is to be checked before use.

Routine checking. In a modern anaesthetic environment, the anaesthetist will be using an anaesthetic machine, a ventilator, a variety of i.v. infusion methods and an increasing number of monitors. All need to be checked before use, although much is extremely reliable. Check lists are becoming popular and the Australian Faculty of Anaesthetists has published a comprehensive list for anaesthetic machines (Faculty Documents, 1984). The main sections are easy to remember: Gas Supplies; Flowmeters; Vaporizers; Pre-circuit Leaks; Breathing System; Circle Absorber. However, the 61 steps into which these six sections are divided cannot be memorized easily and the objective of always using a check list before starting an operating list may only be achieved if the full check list is written down and available.

Monitoring

Close and continuous monitoring of the anaesthetized patient is an obvious goal in improving safety. What is of concern is the profusion of electrical devices which can now be used to monitor an increasing number of physiological and pharmacological parameters. The addition of another transducer with its associated controls, displays and alarms may not increase safety. Those interested might wish to compare the

TABLE V. *Minimal monitoring standards for anaesthesia* (*Harvard recommendations* (*Eichhorn et al., 1986*))

(1) Continuous presence of anaesthetist throughout procedure.

(2) Arterial pressure and heart rate measured at least every 5 min where not clinically impractical.

(3) An ECG to be displayed continuously, where not clinically impractical.

(4) Continuous monitoring of:
  (a) Ventilation. One of: palpation or observation of reservoir bag, auscultation of breath sounds, monitoring of ventilatory gases such as carbon dioxide or monitoring of expired gas flow.
  (b) Circulation. One of: palpation of a pulse, auscultation of heart sounds, monitoring of direct arterial pressure, pulse plethysmography/arterial saturation or ultrasound pulse monitoring.
The monitoring should consist of at least one method each for ventilation and circulation.

(5) Breathing system disconnection monitoring when ventilation is controlled.

(6) Oxygen analyser. During every anaesthetic involving the use of an anaesthetic machine, the oxygen concentration in the breathing system to be monitored with a device incorporating a low concentration alarm.

(7) Temperature. Facilities to measure body temperature to be readily available.

profusion of dials, switches and alarms in the cockpit of an aircraft such as the Boeing 747 with the relative simplicity of the company's later aircraft such as the 767.

There are moves to introduce acceptable minimal standards of monitoring for all anaesthetized patients. Eichhorn and his colleagues (1986) have described the system currently used in the Harvard group of hospitals. The system is summarized in table V. It is useful as a benchmark for others to evaluate and modify. The author's own preference is to add, as with temperature monitoring, an option that neuromuscular transmission can be checked in any anaesthetic location. This should reduce substantially the incidence of ventilatory problems following misuse or inadequate antagonism of neuromuscular blockers.

THE ROLE OF RESEARCH

Research into anaesthetic safety is an essential part of the education process. Current efforts are directed at the nature of anaesthetic hazards and, increasingly, at their incidence. The study being conducted by the Association of Anaesthetists of Great Britain and Ireland and the Association of Surgeons is welcome, not only for looking at anaesthetic and surgical factors, but because it will also provide the denominator and thereby permit an overall assessment of risk. What are also needed are studies of the effectiveness of education in safety matters. Will there be fewer anaesthetic deaths or fewer critical incidents as a result of an education programme, and which elements of such programmes are the most effective? Research is also needed into the use of such educational methods as the use of stimulators, which may well give insight to the psychological factors in anaesthetic mishaps.

CONCLUSION

Anaesthesia has a good safety record but, as with all human endeavour, accidents do occur. Investigation of these untoward events has often concentrated on determining what occurred and whether or not the accident was inevitable. In designing an education programme to reduce avoidable accidents, attention should be directed to three areas: what are the common patterns of events; what factors precipitate them, including the human considerations in the anaesthetic and surgical team; and, finally, what strategies can be devised to prevent (preferably), recognize and treat them?

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PROCEEDINGS OF THE ANAESTHETIC RESEARCH SOCIETY

OXFORD MEETING

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(The name of the author presenting the paper is shown in bold type. *Indicates non-member.)

ALVEOLAR DEADSPACE IN CYANOTIC HEART DISEASE

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Intracardiac right-to-left (RL) shunting causes arterial hypoxia. Also, because arterial $P\text{CO}_2$ is increased above the value of pulmonary end capillary $P\text{CO}_2$, there is an increase in the alveolar deadspace fraction ($V\text{D}^{alv}/V\text{T}^{alv}$). This increased deadspace is "apparent" in as far as it does not represent wasted ventilation of any compartment, but it is real in that an increased minute ventilation is needed in order to maintain a normal Pa_{CO_2}.

Fifty-seven children undergoing cardiac surgery were investigated. Carbon dioxide single breath tests were obtained using an on-line computer which received signals for expired $P\text{CO}_2$ and airway flow and pressure from the ventilator and carbon dioxide analyser (Fletcher, Niklason and Drefeldt, 1986). Blood-gases were sampled at the same time in order to calculate $V\text{D}^{alv}/V\text{T}^{alv}$. All measurements were obtained with the patient supine during undisturbed fentanyl–nitrous oxide anaesthesia. $F\text{I}_{\text{O}_2}$ was 0.50.

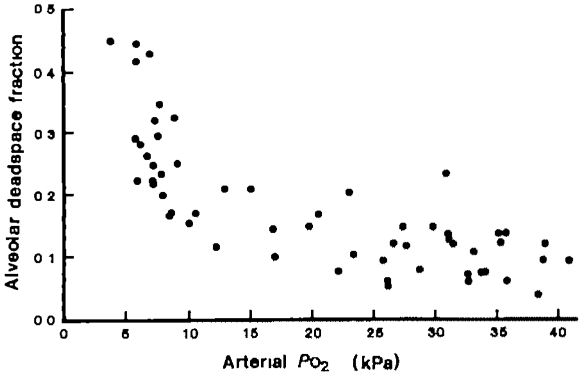

FIG. 1. $V\text{D}^{alv}/V\text{T}^{alv}$ related to Pa_{O_2}.

Figure 1 shows $V\text{D}^{alv}/V\text{T}^{alv}$ related to Pa_{O_2}. In children with normal pulmonary circulation and in many with left-to-right shunting, Pa_{O_2} was greater than 30 kPa. These children had $V\text{D}^{alv}/V\text{T}^{alv}$ values of about 0.1. Children with pure R–L shunts and mixed shunts had low Pa_{O_2} and large alveolar deadspaces. There was a reciprocal relationship between $V\text{D}^{alv}/V\text{T}^{alv}$ and Pa_{O_2}: $V\text{D}^{alv}/V\text{T}^{alv} = 0.06 + 1.54/Pa_{\text{O}_2}$ (kPa) ($r = 0.85$; $P < 0.0001$).

The relationship between $V\text{D}^{alv}/V\text{T}^{alv}$ and Pa_{O_2} agrees qualitatively with that to be expected from the relationships between shunt fraction and Pa_{O_2} (Benatar, Hewlett and Nunn, 1973) and between shunt fraction and $V\text{D}^{alv}/V\text{T}^{alv}$.

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INTERRUPTED HIGH FREQUENCY VENTILATION (IHFV)

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Clinicians are becoming aware and concerned about the dangers of high frequency ventilation (HFV) and oscillation (HFO) because of large sustained increases in lung volume, PEEP effect, with potential alveolar damage and circulatory impairment.

A new technique of ventilation is described, Interrupted High Frequency Ventilation (IHFV), which consists of short periods of HFV or HFO, interrupted by short stoppages of ventilation which allows the lung to empty to FRC or to any desired value of PEEP. Thus, the increase in the lung volume during HFV or HFO, which hitherto has been a problem, becomes a substantial additional expired volume to improve carbon dioxide scavenging.

Any ventilator modified to interrupt the ventilation from 0 to 20 times per minute (i.p.m.) with a variable stoppage period for expiration (interruption pause period, IPP), is suitable for IHFV. A simple arrangement to modify a high frequency jet ventilator is illustrated in figure 2.

Observations were made on five large anaesthetized paralysed dogs, with normal lungs. Nebulized carbachol was applied through the airways to simulate respiratory distress syndrome (Kaiser et al., 1985). A valveless all-purpose

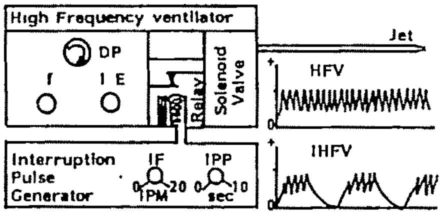

FIG. 2. Modification of a high frequency jet ventilator.

ventilator was modified to provide IHFV. Ventilation frequencies from 10 to 300 b.p.m. were applied and also interrupted at a freqency (IF) of 7 i.p.m. with a 3-s IPP.

During IHFV there was a 35–50% reduction in mean airway pressure which was greatest during carbachol-induced changes. The end-expiratory pressure could be returned to 0 during the pauses. The increase in lung volume (e.g. up to 1.11) was discharged and measured during the pauses, eliminating sustained lung distension. There was a significant reduction in Pa_{CO_2}. Alveolar gas was expired during the pauses, which allowed the measurement of the end-tidal carbon dioxide concentration.

Lung model experiments showed reductions in compliance pressure—that is alveolar pressure which returned to zero during the interruption pauses.

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LOW-FLOW N_2O/O_2 AND N_2/O_2 CIRCLE SYSTEMS

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The use of low-flow breathing systems for the delivery of nitrous oxide in oxygen mixtures during anaesthesia is complicated by time-dependent changes in the rate of exchange of gases between the patient and the system, introducing some difficulty in predicting $F\text{I}_{O_2}$. Earlier work (Allison, Wishart and Spence, 1980) suggested that a fresh gas flow (FGF) of 50% nitrous oxide in oxygen 1 litre min^{-1} could provide a practicable approach to maintenance of an acceptable concentration of oxygen within a circle system. The present investigation examines further the behaviour of this system.

We studied adults presenting for elective general surgery, either breathing spontaneously or receiving IPPV during anaesthesia from a circle breathing system. The fresh gas was either 50% nitrous oxide in oxygen or 50% nitrogen in oxygen by random allocation, in addition to randomly assigned halothane or isoflurane. FGF was 4 litre min^{-1} for 10 min and thereafter reduced to 1 litre min^{-1} for the remainder of the anaesthetic. Concentrations of oxygen in the expiratory limb of the breathing system were measured using a fuel cell oxygen analyser and recorded at 5-min intervals.

For both gas mixtures there were no significant differences in mean concentrations at given times between the spontaneously breathing and IPPV groups. For patients receiving nitrous oxide in oxygen the oxygen concentration (vol %) decreased from 46.4 ± 1.9 (mean ± SD; $n = 99$) 5 min after reducing the FGF, to 39.1 ± 2.2 ($n = 22$) over the next 75 min; the minimum oxygen concentration observed for any patient over this time was 28%. For patients receiving nitrogen in oxygen the oxygen concentration decreased from 40.3 ± 2.9 ($n = 98$) to 31.5 ± 3.8 ($n = 17$) over the same intervals and the minimum oxygen concentration observed for any patient was 22%.

These results suggest that continued oxygen uptake over the period of observation is involved in the stabilization of oxygen concentration within the nitrous oxide in oxygen system.

ACKNOWLEDGEMENT

This work was supported by a grant from the Scottish Hospital Endowments Research Trust.

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EFFECTS OF NALBUPHINE HYDROCHLORIDE AND NALOXONE ON THE VENTILATORY RESPONSE TO CARBON DIOXIDE IN VOLUNTEERS

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Maximum ventilatory depression may occur following nalbuphine 30 mg/70 kg i.v. (Romagnoli and Keats, 1980) or 0.15 mg kg^{-1} (Gal, DiFazio and Moscicki, 1982).

The ventilatory effects of nalbuphine and naloxone were investigated in six healthy, non-smoking, male volunteers (mean age 25.5 (5.6) yr, mean VC 6.23 (0.85) litre) in a single-blind laboratory study. At the same time of day, on 4 separate days each, at least 4 days apart, volunteers received placebo (0.9% sodium chloride) and three randomly assigned doses of nalbuphine (15, 30 and 60 mg/70 kg), administered i.v. over 5 min. Samples were taken for measurement of serum nalbuphine concentrations at times −60 and 30 and 60 min after the dose. Rebreathing procedures were carried out using 6% carbon dioxide in oxygen from a bag (volume adjusted to half the VC) at −30 min (control), 30 min (30 min after placebo or nalbuphine), 90 min (immediately after naloxone 0.4 mg/70 kg i.v.), and 150 min (1 h after naloxone). Each rebreathing procedure was performed twice in both the lying and sitting positions. Flow, tidal volume (wedge spirometer), airway pressure (low pressure transducer, range ± 25 cm H_2O) and end-tidal carbon dioxide (Engström Eliza) signals were displayed on a u.v. chart recorder (Bell & Howell). For each breath $T\text{I}$, $T\text{E}$, $P\text{E}_{CO_2}$ and $V\text{T}$ were measured with a digitizer linked to a microcomputer (BBC). Occlusion pressures were recorded onto magnetic tape and replayed onto u.v. paper. Occlusion pressures were measured at 100 ms after the airway pressure had become less than −0.1 kPa ($Po_{0.1}$). Systolic and diastolic arterial pressures and heart rate were recorded at 15-min intervals (Critikon Dinamap). Side effects were noted and sedation assessed with an LAS for sedation (between alert and drowsy) at times −30, 30 and 150 min. Results were expressed as mean (SD) of values at 7 kPa and statistical significance was tested for by paired t test.

The mean depression of ventilation and $P\mathrm{o}_{0.1}$ was significant ($P < 0.001$), compared with control, at 30 min after each dose of nalbuphine. We could not demonstrate any difference in the ventilatory depression caused by any of the doses of nalbuphine. Naloxone significantly increased ($P < 0.05$) the ventilation in subjects who received 15 mg/70 kg (sitting and lying) and 30 mg/70 kg (lying). Maximum sedation and vomiting was most frequent following 30 mg/70 kg. Cardiovascular stability was maintained in all subjects throughout the study.

An effect maximum for ventilatory depression was shown following 15 mg/70 kg. Naloxone failed to reverse the depression at the highest nalbuphine dose.

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PROPOFOL DEPRESSES CAROTID BODY CHEMORECEPTOR DISCHARGE IN RABBITS AND CATS

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Induction of anaesthesia with propofol is often followed by a period of apnoea lasting 30 s or more (Walmsley, McLeod and Ponte, 1986). In a recent study, Taylor and others (1986) showed that propofol caused a more profound and more prolonged ventilatory depression than thiopentone in equipotent inducing doses. We examined the effect of propofol upon the discharge of single chemoreceptor afferent fibres in the sinus nerve of four New Zealand White rabbits and three cats (2.9–3.7 kg). Animals were anaesthetized with pentobarbitone 4 mg $\mathrm{kg^{-1}\ h^{-1}}$ i.v. and the neck dissected to expose the left carotid artery. The sinus nerve was cut proximally and dissected under mineral oil for unipolar recordings (Ponte and Sadler, 1985). The lingual artery was cannulated for direct infusion of propofol (10 mg $\mathrm{ml^{-1}}$) to the carotid sinus, proximally to the carotid body. Constant rates of infusion were used, ranging between 0.1 and 1 mg $\mathrm{kg^{-1}\ min^{-1}}$. In all animals a dose-dependent depression of activity was observed, which was rapid in onset and rapid in recovery after stopping the infusion. In normoxia, the effect started at 0.3 mg $\mathrm{kg^{-1}\ min^{-1}}$ and activity was totally abolished at 1 mg $\mathrm{kg^{-1}\ min^{-1}}$. The depressant effect of propofol was less marked in hypoxia ($P\mathrm{a}_{\mathrm{O}_2}$ 40 mm Hg).

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COMPARISON OF THE MAGILL AND LACK ANAESTHETIC BREATHING SYSTEMS IN ANAESTHETIZED PATIENTS

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The fresh gas flow rate required to prevent rebreathing in the Magill and Lack breathing systems has been the subject of controversy (Conway et al., 1976; Barnes, Conway and Purcell, 1980; Humphrey, 1982). Humphrey (1982) suggested that a fresh gas flow rate of 51 ml $\mathrm{kg^{-1}\ min^{-1}}$ in the Lack system and 71 ml $\mathrm{kg^{-1}\ min^{-1}}$ in the Magill system would just induce rebreathing. This is considerably less than the previous recommendation with respect to the Lack breathing system.

In this study, 24 adults (ASA grade I) undergoing routine surgery were studied. They were allocated randomly to one of four groups, Magill system, 50 and 70 ml $\mathrm{kg^{-1}\ min^{-1}}$ and Lack system, 50 and 70 ml $\mathrm{kg^{-1}\ min^{-1}}$. Each subject was premedicated with diazepam by mouth 2 h before operation. Anaesthesia was induced with thiopentone 5 mg $\mathrm{kg^{-1}}$, suxamethonium 150 mg was administered and nasotracheal intubation performed. The subjects were allowed to breathe spontaneously a mixture of 1% halothane in oxygen–nitrous oxide at a relatively high fresh gas flow until a steady state had been achieved, indicated by a constant minute ventilation. The fresh gas flow rate was then reduced to that required for the group to which the patient had been allocated. Minute ventilation end-tidal and inspired carbon dioxide concentrations were measured and recorded.

At the high fresh gas flow rate, one patient in the Magill group had an increase in inspired carbon dioxide concentration. At the lower fresh gas flow rate all but one subject in each group had an increase in inspired carbon dioxide concentration. The majority of patients in both groups had an increase in end-tidal carbon dioxide concentration and an increase in minute ventilation. We conclude that rebreathing was occurring in both the Magill and Lack breathing systems when the fresh gas inflow was 50 ml $\mathrm{kg^{-1}\ min^{-1}}$. Rebreathing, indicated by an increase in inspired carbon dioxide concentration, did not occur in either breathing system in the majority of patients, when fresh gas inflow was 70 ml $\mathrm{kg^{-1}\ min^{-1}}$. However, small changes in minute ventilation and end-tidal carbon dioxide concentration were detected.

In this study a fresh gas flow rate of 70 ml $\mathrm{kg^{-1}\ min^{-1}}$ approximated to alveolar ventilation. In the Magill and Lack breathing systems, fresh gas inflow in excess of 70 ml $\mathrm{kg^{-1}\ min^{-1}}$ is required to prevent rebreathing. This supports previous recommendations for fresh gas flow rates.

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COMPARISON OF THE EFFECTS OF CONVENTIONAL VENTILATION AND HIGH FREQUENCY OSCILLATION ON HYALINE MEMBRANE FORMATION IN A RABBIT MODEL OF NEONATAL RESPIRATORY DISTRESS SYNDROME

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The neonatal respiratory distress syndrome is characterized by surfactant deficiency and capillary damage resulting in increased permeability. Regional differences in lung compliance may produce stresses between adjacent lung units during ventilation, resulting in haemorrhage and hyaline membrane formation. If repeated alveolar collapse and re-expansion could be avoided, it may be possible to limit hyaline membrane formation. The use of positive end-expiratory pressure (PEEP) with conventional mechanical ventilation (CMV) or high frequency oscillation (HFO) (Hamilton et al., 1983) has been advocated to prevent this damage.

A rabbit model of neonatal respiratory distress syndrome (NRDS) was produced by saline lavage of the lungs (Lachmann, Robertson and Vogel, 1980). This produced a marked change in the compliance curve with the development of an inflection point at a pressure of 8–12 mm Hg. Three groups of eight rabbits were ventilated with: group 1, CMV with low PEEP (5 mm Hg below the inflection pressure); group 2, CMV with high PEEP (equal to the inflection pressure); group 3, high frequency oscillation (HFO). Mean airway pressures were kept at 14–16 mm Hg in all three groups. Animals completing the 5-h procedure numbered five in group 1, six in group 2 and five in group 3, early demise usually being caused by metabolic acidosis. With 100% oxygen the mean Po_2 at 2 h after lavage were: group 1, 15.2 ± 8.3 kPa; group 2, 39.6 ± 12.2 kPa; group 3, 67.7 ± 14.5 kPa. Measurements of end-expiratory lung volumes were as follows: group 1, 0 ± 1.5 ml; group 2, 34.9 ± 12.2 ml; group 3, 54.6 ± 12.1 ml.

Histological examination of the lungs revealed significantly less hyaline membrane formation in groups 2 and 3 compared with group 1 ($P \leqslant 0.001$).

Thus, prevention of collapse by either high PEEP or HFO, produces a significant improvement in pulmonary pathology. HFO appeared to show some added advantage by improving the post-lavage compliance curves of some of the animals.

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ONSET AND OFFSET—AN EXAMINATION OF SEVERAL NEUROMUSCULAR BLOCKERS

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Neuromuscular blocking agents are regularly examined using techniques where either increasing cumulative concentrations are given, or single discrete doses are administered, each followed by full recovery. In clinical situations it has been observed that the degree of fade is different during spontaneous offset than during onset of blockade. It was therefore decided to test if neuromuscular blockade was the same during cumulative onset as during cumulative offset.

The rat phrenic nerve–diaphragm preparation was used, suspended in Krebs solution at 37 °C, aerated with 5% carbon dioxide in oxygen. Isometric contractions evoked by 0.2-ms supramaximal square-wave stimuli delivered at a rate of 0.1 Hz to the phrenic nerve were recorded on a Grass polygraph. A low concentration of neuromuscular blocker in pre-oxygenated Krebs solution at 37 °C was introduced to the bath. Once a steady state had been reached (20 min) the bathing solution was changed for fresh, prewarmed, preoxygenated Krebs containing a higher concentration of blocker. This was repeated until approximately 80% twitch height inhibition was reached, followed by the same concentrations in a reducing sequence.

TABLE I. *$ED_{50} \pm SEM$ ($\times 10^{-6}$ mol litre^{-1}, or dose units)*

Agent	Ascending	Descending
Tubocurarine	0.85 ± 0.05	0.83 ± 0.05
Pancuronium	3.08 ± 0.09	3.21 ± 0.17
Alcuronium	1.36 ± 0.09	1.33 ± 0.10
Panc. + Tubo. mixture	0.70 ± 0.03	0.67 ± 0.04

Preparations were used in pairs, the neuromuscular blocker being administered to one and the second being used as an exact time matched control. Six preparations were used for each agent. Pancuronium, tubocurarine, alcuronium and a pancuronium–tubocurarine mixture were studied. The concentrations of individual neuromuscular blocker were expressed as molarity, and those of the mixture in dose units (Pollard and Jones, 1983). The percent twitch height inhibition was calculated for each concentration of blocker, together with the percent decay in the matched control preparation at the same time. The percent reduction in twitch height in the control preparation was then subtracted from that produced by the drug. Individual log concentration response graphs were plotted and EC_{50} recorded for each line (table I).

For each agent (or combination) the ascending EC_{50} was close in value to the descending EC_{50} and there was no significant difference between them (paired *t* test). There was also no significant difference between the slopes. It is concluded, therefore, that the ascending and descending lines are coincidental and the percent depression of twitch height is directly proportional to the concentration of neuromuscular blocker, with no hysteresis.

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EXTRADURAL AND INTRAPERITONEAL SUFENTANIL IN THE RAT: ANALGESIA, ANTAGONISM AND PLASMA DRUG CONCENTRATIONS

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Sufentanil is an opioid analgesic with high lipid solubility and affinity for the mu-receptor (Leysen, Gommeren and Niemegeers, 1983). These characteristics make sufentanil an attractive choice for extradural use, with the prospect of rapid onset and few central side effects. The present study was designed to compare extradural and i.p. sufentanil in the rat.

Epidural catheters (deadspace 5 µl) were chronically implanted in male Sprague–Dawley rats weighing 250–350 g. Extradural doses of sufentanil or naloxone were delivered in 80 µl and flushed with 20 µl of 0.9% sodium chloride. I.p. doses were delivered in 1 ml. For extradural and i.p. sufentanil, dose–response studies were performed for tail flick and hot plate. The electrically heated water bath and metal plate were kept at 54 ± 1 °C and cut-off time in the absence of response was 10 s. Animals were tested before injection of sufentanil, at 3 and 5 min after administration, then at 5-min intervals for 1 h and then at 10-min intervals until the response returned to control time. Responses were expressed as percent of maximal possible effect (%MPE):

$$\%\text{MPE} = \frac{\text{postdrug latency} - \text{predrug latency}}{\text{cut-off time} - \text{predrug latency}} \times 100$$

Areas under the time–response curves (AUC) were measured. Also recorded were attempts to escape or vocalize during paw pinch, and the animals were observed for rigidity and ventilatory depression. Antagonism by extradural and i.p. naloxone of extradural sufentanil at an approximate ED$_{50}$ dose for tail flick was also assessed. Blood was collected for radioimmunoassay of sufentanil (Michiels, Hendricks and Heykants, 1982). Extradural catheters were injected with indian ink and examined histologically.

None of the 40 animals with an extradural catheter showed signs of neurological impairment and histological examination revealed four catheters (10%) to be intrathecal. For the tail flick response the %MPE and AUC were greater after extradural compared with i.p. administration of sufentanil. Hot plate responses were less different for the two routes, and this was reflected in the ED$_{50}$ values for the log dose–response curves. There was no evidence for segmental analgesia and rigidity and ventilatory depression were found after administration by both routes. Naloxone given by extradural injection was more potent than i.p. naloxone for inhibiting the effect of extradural sufentanil on the tail flick response. Plasma concentrations of sufentanil were lower after extradural compared with i.p. administration, but the difference was not statistically significant.

These findings support the theory that there is initial relative compartmentalization of sufentanil after extradural administration. However, intravascular absorption may account for some effects.

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ONSET OF ATRACURIUM-INDUCED BLOCKADE IN THE MUSCLES OF THE FACE: ORBICULARIS OCULI AND ADDUCTOR POLLICIS COMPARED

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On occasions, the facial muscles may be more accessible than the muscles of the hand when monitoring the degree of neuromuscular blockade during anaesthesia. Stiffel and colleagues (1980) have demonstrated that the facial muscles are less sensitive to tubocurarine and suxamethonium than the muscles of the hand. The orbicularis oculi recovers from atracurium blockade more rapidly than the adductor pollicis when the force of contraction is measured (Caffrey, Warren and Becker, 1986). Electromyography is being increasingly applied routinely during anaesthesia and may be more appropriate when stabilization of a force transducer would be difficult: for example, on the face. It would be valuable to compare the electromyographic response (EMG) of the orbicularis oculi with that of the adductor pollicis during onset of blockade with atracurium.

Ten adults undergoing elective surgery were investigated with Ethical Committee approval. A standard anaesthetic technique using thiopentone 5–7 mg kg^{-1}, fentanyl 2–3 µg kg^{-1} and 67% nitrous oxide in oxygen was used. Ventilation was adjusted to produce normocapnia. No volatile agent was used. The ulnar and facial nerves were stimulated simultaneously with supramaximal pulses of 0.2 ms duration every 20 s. The EMG were recorded over the adductor pollicis and the orbicularis oculi via ECG-type electrodes using a two-channel electromyograph (Dantec 2000M) and the peak-to-peak amplitude was measured using cursors with maximum discrimination of 2 µv.

Following induction of anaesthesia, three stable control measurements were obtained and atracurium 0.23 mg kg^{-1} was administered i.v. Measurements were continued until maximum blockade was observed. Student's paired *t* test was used to analyse differences between muscles (table II).

TABLE II. *Maximum % depression of EMG amplitude and time taken to reach 50% and maximum blockade (mean ± SEM)*

	Adductor pollicis	Orbicularis oculi
Max. % block	91.2 ± 1.7	69.2 ± 4.9
Time to 50 % block (min)	2.3 ± 0.2	2.5 ± 0.4
Time to max. block (min)	5.9 ± 0.4	4.8 ± 0.2

Maximum blockade was significantly greater in the adductor pollicis compared with the orbicularis oculi ($P < 0.005$). The orbicularis oculi reached maximum blockade faster than the adductor pollicis ($P < 0.02$), but the time taken to reach 50% amplitude depression was similar ($P > 0.05$).

These data suggest that measurement of the EMG of the orbicularis oculi, in common with measurement of the force of contraction, underestimates the degree of neuromuscular blockade in relation to the adductor pollicis.

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TETANIC FADE DURING NEUROMUSCULAR BLOCKADE PRODUCED BY ATRACURIUM IN THE RAT DIAPHRAGM PREPARATION

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The phenomenon of tetanic fade (a progressive decline in the tetanic tension in the presence of a non-depolarizing neuromuscular blocking agent) has been demonstrated in both man and experimental animals (Bowman and Webb, 1976; Madden, Hughes and Payne, 1983). Tetanic fade is a function not only of the degree of curarization, but also of the frequency and duration of the tetanic response. Recently, it has been shown that different nicotinic antagonists may produce different amounts of tetanic fade and that atracurium produces a greater tetanic fade than tubocurarine or pancuronium in the isolated hemidiaphragm preparation of the rat (Gibb and Marshall, 1986).

In the present investigation, we have studied the effect of atracurium on the indirectly-elicited twitch and tetanic tensions to further analyse and measure, quantitatively, the atracurium-induced tetanic fade and peak tetanic depression in the rat hemidiaphragm preparation.

The phrenic nerve was stimulated at 0.2–100 Hz, for 1–5 s duration, with 2–5 V (supramaximal) and 0.1–0.2 ms pulse duration. Tetanic fade (TF) was measured as the difference between the peak tetanic tension (*T*p) and the end tetanic tension (*T*e), expressed as a percentage of the whole tetanic tension:

$$\mathrm{TF} = \left(\frac{Tp - Te}{Tp}\right) \times 100$$

Atracurium 0.1–100 μmol litre⁻¹, reduced the amplitude of the twitch tension in a concentration-dependent manner. The mean IC_{50} values (concentration to produce 50% maximum inhibition) of atracurium-induced depression of twitch tension was 0.9 ± 0.1 μmol litre⁻¹ (mean ± SEM; $n = 8$). Atracurium 10 μmol litre⁻¹, which depressed the single twitch tension by 80%, reduced the contractions produced by nerve stimulation, at 1–100 Hz, in a frequency-dependent manner. The peak tetanic tension (at 50 Hz for 1 s), tetanic tension fade and peak tetanic tension depression (TD) values, in the absence and presence of atracurium 10 μmol litre⁻¹, for 20 s exposure, are shown in table III.

Complete tetanic fade occurred within 30 ± 5 s, whereas peak tetanic depression occurred at 3.5 ± 0.3 min. It was concluded that atracurium produced a profound tetanic fade, relative to twitch or tetanic tension depression, suggesting a strong prejunctional inhibitory effect at the neuromuscular junction.

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TABLE III. *Peak tetanic tension, tetanic fade and peak tetanic tension depression (means ± SEM;* n = *8), produced by phrenic nerve stimulation at 50 Hz for 1 s duration, in the presence of atracurium 10 μmol litre⁻¹.* $^*P < 0.05$

Control			Atracurium 10 μmol litre⁻¹			
*T*p (g)	*T*e (g)	TF (%)	*T*p (g)	*T*e (g)	TF (%)	TD (%)
5.6 ± 0.4	4.8 ± 0.5	14 ± 1.6	4.2 ± 0.3	1.0 ± 0.1	*76 ± 3.2	*25 ± 2.1

STELLATE GANGLION BLOCKADE WITH BUPIVACAINE: EFFECT OF VOLUME ON EXTENT OF SYMPATHETIC BLOCKADE

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Stellate ganglion blockade with local anaesthetic agents has been proposed for a variety of pain states and medical conditions using volumes of local anaesthetic ranging from 5 to 20 ml. A study was performed to assess the influence of volume injected on the extent of block as assessed by liquid crystal thermography: sympathetic blockade produces vasodilatation which results in an increase in skin temperature.

Twenty patients with chronic pain from a variety of causes affecting the head, neck and arm were allocated at random to receive either 10 or 20 ml of 0.5% bupivacaine (plain) solution injected onto the precervical fascia at the level of the 6th cervical vertebra. The method used was modified from Moore (1954). Successful cranial sympathetic blockade was confirmed by an ipsilateral Horner's syndrome. Thermography of the hands, arms and chest wall was performed before and 30 min after the injection. An assessment was made at this later time of the presence of the following side effects indicating unwanted spread of solution: hoarseness, arm weakness or paraesthesiae and dysphagia.

Cranial sympathetic blockade was confirmed in all patients. Injection of 20 ml of solution was required to produce sympathetic blockade of the arm and hand; 10 ml was associated with statistically significantly less cervical sympathetic blockade (chi-squared test). The larger volume was associated with a significant incidence of hoarseness, and a tendency to dysphagia. Spread of solution onto the cervical somatic roots occurred in only one patient. Thoracic sympathetic block did not occur in any patient.

In the performance of stellate ganglion injection the extent of sympathetic blockade can be predicted from the volume used. Larger volumes are associated with an increased incidence of side effects.

Benefit has been claimed for such conditions as thoracic post-herpetic neuralgia (Milligan and Nash, 1985). Our results suggest that this may result from "placebo" or systemic absorption of local anaesthetic rather than sympathetic blockade.

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PHARMACOKINETICS OF MIDAZOLAM INFUSION FOLLOWING OPEN HEART SURGERY IN PAEDIATRIC PATIENTS

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Midazolam infusions provide stable plasma concentrations and good sedation with mininal cumulation and prompt recovery in adults who are normal metabolizers requiring a short period of ventilatory support following open heart surgery. Clearance has been shown to be greater and elimination half-life shorter in children than in adults following CPB (Mathews et al., 1987).

In this study nine children (excluding babies younger than 3 months) in the cardiac recovery ward, received a bolus of midazolam 0.05 mg kg^{-1} followed immediately by an infusion of 0.05 mg kg^{-1} h^{-1} via a central catheter. No benzodiazepine had been administered before or during operation. Morphine 0.2–0.5 mg i.v. was prescribed as required and no neuromuscular blocker was required.

Aliquots of 1 ml of arterial blood were drawn five times during the first 1 h and 2-hourly for the first 12 h of therapy, with further samples taken before discontinuing the infusion and at 2, 4, 6, 12 and 24 h later. Plasma was analysed for total plasma midazolam concentration using GLC. The coefficient of variation of the method was 2–4%.

The average age and weight of the children (± SEM) were 4.7 ± 0.76 yr and 14.9 ± 1.02 kg, respectively. Mean plasma concentrations of midazolam 80–100 ng ml^{-1} were rapidly achieved and maintained during the infusion (mean duration 16 ± 0.5 h). Eight children were considered to be adequately sedated with an average of morphine 8.2 ± 1.65 mg during the infusion period. One 20-kg child who was very restless had midazolam concentrations ranging from 50 to 70 ng ml^{-1} and required morphine 43.5 mg over 17 h of therapy.

Two hours after discontinuation of the infusion, mean plasma concentrations had decreased to 38 ± 6.4 ng ml^{-1} and no midazolam was detected in any patient 24 h after discontinuation. Recovery was prompt in all children. Individual clearances calculated from C^{ss} averaged 575 ± 73.5 ml kg^{-1} h^{-1}. Terminal half-lives, calculated from individual decay curves, averaged 3.1 ± 0.48 h.

The plateau values were similar to those producing adequate sedation in adults (Allonen, Ziegler and Klotz, 1981), but lower than those found necessary for sedation in paediatric patients following cardiac surgery (Lloyd-Thomas and Booker, 1986). The pharmacokinetic values are similar to those found with single bolus studies in children following CPB (Mathews et al., 1987). Children have a higher clearance and shorter $T_{\frac{1}{2}}^{\beta}$ than adults receiving a midazolam infusion in a similar situation.

Midazolam infusions with intermittent morphine provide adequate sedation in most children following open heart surgery with minimal cumulation and rapid recovery.

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INFLUENCE OF FASTING ON POSTOPERATIVE HEADACHE IN DAY-STAY PATIENTS

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Postoperative headache following minor gynaecological surgery can be a distressing complication of anaesthesia (McDowell, Dundee and Pandit, 1970) particularly in the day-stay setting. The incidence may be influenced by fasting, inhalation anaesthetic agents or susceptibility to headache. Millar, Wishart and Nimmo (1983) have questioned the necessity of 4-h fasting before elective surgery. The influence of some of these factors on postoperative headache has been studied.

Unpremedicated fit women, scheduled for minor gynaecological operations were allocated to four groups as follows: control ($n = 50$) = overnight fast; breakfast ($n = 50$) = light breakfast 2 h before induction; dextrose ($n = 20$) = overnight fast, 5% dextrose 500 ml during operation; saline ($n = 20$) = overnight fast, 0.9% saline 500 ml during operation.

Anaesthesia was induced with methohexitone 1.5 mg kg^{-1} and maintained with nitrous oxide and halothane in oxygen. After operation the incidence and severity of headache upon awakening (early) and between 1 and 4 h (late) was noted.

TABLE IV. % *Incidence, timing and severity of headache.* **P < 0.05 compared with controls*

Group	*n*	Total	Early	Severe
All patients				
Control	50	44	42	22
Breakfast	50	20*	10*	2*
Dextrose	20	45	20*	15
Saline	20	35	10*	10
Headache-prone				
Control	16	69	56	38
Breakfast	10	20*	10*	10*

The maximum incidence of vomiting was 5%.

The results (table IV) indicate that the incidence of headache may be significantly reduced in patients given a light breakfast of a cup of tea and a slice of toast. This reduction is more marked in patients prone to headache. Fluid therapy decreased early headache, but not the overall incidence of headache.

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OPEN LOOP CONTROL OF PROPOFOL INFUSIONS

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For i.v. infusion of an anaesthetic drug, the rapid attainment of a steady plasma concentration provides many advantages. Various strategies have been tried, but those using a combination of single dose with fixed rate infusions almost always result in a period of excessive plasma concentration followed by a period in which the plasma concentration is less than the desired final value.

Using a three-compartment pharmacokinetic model, a computer program was written to calculate the infusion rates needed to attain and maintain a constant predetermined plasma concentration. The equations were based on those used for computer controlled fentanyl infusions (Alvis et al., 1985). The BBC microcomputer running the program was interfaced with an IMED 929 infusion pump. Our initial studies on the application of such a program to propofol infusions used pharmacokinetic parameters derived from single dose injections (Kay et al., 1986), but these resulted in high initial plasma concentrations and subsequent values which were less than that desired. In the present study we used parameters derived from our own and other pharmacokinetic studies (Cockshott et al., 1987) using continuous infusions.

Eight healthy patients, aged between 35 and 65 yr, undergoing body surface operations were premedicated with morphine sulphate 0.15 mg kg^{-1}. Anaesthesia was induced with propofol at a rate set by the program and, following tracheal intubation, anaesthesia was maintained for up to 120 min with the propofol infusion and 67% nitrous oxide in oxygen. The patients breathed spontaneously through a Mapleson A system. Venous blood samples for whole-blood propofol estimations using the HPLC/fluorescence method, were taken from the antecubital fossa of the arm not receiving the infusion.

TABLE V. *Whole-blood propofol concentration* ($\mu g\ ml^{-1}$) *during computer controlled infusions* (n = *8*)

Time (min)	2	5	10	15	20	30	60	120
Concentration								
Mean	2.16	2.31	2.83	2.93	2.89	2.94	3.19	2.91
SD	1.32	0.93	0.49	0.71	0.81	0.82	0.90	0.51

The target concentration of propofol 3 μg ml^{-1} was approximately reached within 10 min (table V) and maintained at that value thereafter. There was a smooth onset of anaesthesia. The initial mean systolic and diastolic arterial pressures of 141/86 mm Hg (SD 15.2/12.1) gradually decreased over the first 15 min to values of 107/64 mm Hg (SD 10/7.5). The heart rate also decreased over this period from 80 (SD 14.9) to 76 beat min^{-1} (SD 8.7), with a final steady rate of 69 beat min^{-1} (SD 6) from 30 min onwards.

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INTERACTION OF ETHANOL WITH CALCIUM CHANNEL BLOCKERS, NIMODIPINE, NITRENDIPINE AND NIFEDIPINE IN THE RAT ISOLATED VAS DEFERENS PREPARATION

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EFFECT OF LOW DOSE SUFENTANIL PRETREATMENT ON THE INDUCTION DOSE AND CHARACTERISTICS OF TWO BARBITURATES

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Neither thiopentone (STP) nor methohexitone (MX) are ideal induction agents, as both cause dose-related cardiorespiratory depression and the latter excitatory phenomena and respiratory upsets. I.m. opioid premedication reduces the incidence of induction side-effects with MX and decreases STP dose requirements, but can be painful and lead to nausea and vomiting. I.v. pretreatment with fentanyl was shown to be effective before STP (Dundee et al., 1986). Sufentanil is chemically related to fentanyl, with a more rapid onset and

TABLE VI. *Mean induction doses (mg kg^{-1}) and incidence of excitatory phenomena following sufentanil pretreatment* (n = *20*). *Trem. = tremor; tone = hypertonus; IMM = involuntary muscle movement.* *$P < 0.05$; **$P < 0.01$ v. *control group*

Sufentanil dose (μg)	Ind. dose	SD	Range	Trem.	Tone	IMM
(STP) Control	4.44	1.21	2.42–6.29			
1.0	3.94	0.94	2.63–5.75			
2.5	3.23**	0.72	2.00–4.50			
5.0	3.19**	0.78	2.13–5.26			
(MX) Control	1.43	0.20	1.03–1.80	10	6	11
1.0	1.47	0.27	0.94–2.06	7	1*	6
2.5	1.42	0.36	0.79–2.30	3*	2	3**
5.0	1.20*	0.29	0.75–1.69	2**	1*	1**

shorter duration than the latter (Rosow, 1984). This study investigated the effects of sufentanil in various doses before STP or MX induction.

Following Ethical Committee approval, two series of 80 fit, consenting and unpremedicated adult patients scheduled for operations where STP or MX was to be used, were randomly allocated to receive no pretreatment or sufentanil 1, 2.5 or 5 μg i.v. over 2 min. Anaesthesia was induced 2 min later with an initial bolus dose of one of two barbiturates (STP 2 mg kg^{-1} or MX 0.8 mg kg^{-1}) given over 20 s, followed by increments (STP 25 mg or MX 10 mg) every 15 s until loss of verbal contact with the patient occurred. The total dose was taken as the induction dose of the barbiturate. The incidence of excitatory phenomena, and any respiratory effects were recorded, as were changes in systolic arterial pressure during the assessment period (up to 2 min post-induction) in which the patients breathed 66% nitrous oxide in oxygen.

The groups were similar with respect to age, sex, weight, smoking and alcohol usage, although in the 5-μg group of the MX series there was a significant difference in the sex distribution. Allowance was made for this inequality when statistical analysis was carried out using analysis of variance, unpaired *t* tests and Chi-squared tests where appropriate.

A significant reduction in the induction doses of both barbiturates occurred when sufentanil 5 μg was given, compared with control (table VI). The incidence of excitatory phenomena with methohexitone was significantly reduced by sufentanil 2.5 or 5 μg, but respiratory upset was not affected and the occurrence of brief ventilatory depression was increased in the upper dose sufentanil group.

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COMPARISON OF THE ANTI-EMETIC ACTION OF MANUAL AND ELECTRO ACUPUNCTURE WITH THAT OF CYCLIZINE AND METOCLOPRAMIDE

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It has been established beyond reasonable doubt that manual acupuncture (ACP) at P6 point has a definite anti-emetic effect in women undergoing minor operations and premedicated with nalbuphine 10 mg (Dundee et al., 1986). We have compared its efficacy with that of electro ACP and standard anti-emetics.

The selection of patients, ACP point and anaesthetic technique and follow-up have been described by Lynas and others (1986). Nalbuphine 10 mg was used throughout as premedication and adjuvants were given in random order. The anaesthetic technique was intermittent methohexitone supplemented with nitrous oxide. The observers visiting the patients after operation were unaware of the anti-emetics used. It was planned to have equal numbers of patients in each series, but two groups had to be terminated early.

ACP. Manual needling for 5 min: electro ACP with 10 Hz 5 min, 10 Hz 15 min or 1000 Hz 5 min. Doses of anti-emetic were cyclizine 50 mg and metoclopramide 10 mg. All adjuvants were given immediately after premedication.

An unexpectedly high incidence of sickness in the ACP patients, led to an examination of our findings after 50 studies. Emetic sequelae were frequent when 10 Hz was used for 15 min (8/14) and 1000 Hz for 5 min (5/12). Both were

TABLE VII. *Incidence of postoperative emetic sequelae (first 6 h) in groups of 31 women premedicated with nalbuphine 10 mg and adjuvant therapy as shown.* **Includes nausea and vomiting. Compared with control:* †$P > 0.025$; ††$P < 0.01$; ‡$P < 0.0005$

Anti-emetic	Vomiting*	Nausea	Nil
Nil	8	13	10
ACP			
Manual	4	3	24
Electrical	4	2	25
Drugs			
Cyclizine	6	6	19†
Metoclopramide	2	8	21††

discontinued and the remaining series (10 Hz 5 min) continued to 31 observations.

When pooled, the two acupuncture series had significantly ($P < 0.025$) less postoperative sickness (2%) than after the anti-emetics (3%) (table VII). There were no side effects attributable to acupuncture, cyclizine or metoclopramide.

The incidence of postoperative sickness in the control and manual ACP subjects in this study ($n = 31$) is almost identical with that reported by Dundee and others (1986) ($n = 25$). We have again confirmed the finding of Fry (1986) of the anti-emetic effect of P6 stimulation; whereas he obtained 5–30 min of relief of sickness with acupressure, we found 8+ h benefit from both manual and electro ACP.

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WORK CAPACITY OF MALIGNANT HYPERPYREXIA SUSCEPTIBLE INDIVIDUALS

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It is sometimes stated that malignant hyperpyrexia susceptible (MHS) individuals have well developed musculature and are good at sport, but often do not have the muscle power one would expect for the degree of muscle development and have difficulties in co-ordination. Stanec and Stefano (1984) reported a poorer performance by MHS subjects in a standardized exercise test when compared with normal volunteers. Metabolic abnormalities in MH susceptible subjects during exercise have been reported previously (Campbell, Ellis and Evans, 1981), but no formal measurements have been made of work capacity.

Twenty-three patients scheduled for diagnostic muscle biopsy for MH susceptibility were investigated before their biopsy. A heart rate–oxygen consumption ($\dot{V}\text{O}_2$) regression line was constructed for each subject from simultaneous measurements of heart rate and $\dot{V}\text{O}_2$ (Kappagoda, Linden and Stoker, 1974) at rest and at three different levels of exercise. The subject stayed at each work load until a "steady state $\dot{V}\text{O}_2$" had been achieved—$\dot{V}\text{O}_2$ varied by less than 5%. This usually took 4–8 min. The most severe work load was designed to produce a heart rate in excess of 150 beat min^{-1}. Physical work capacity 150 (PWC_{150}) ($\dot{V}\text{O}_2$ at a heart rate of 150 beat min^{-1}) was calculated from the regression line.

Nine subjects were MHS on biopsy and were matched for age (to within 5 yr) and sex with nine of the subjects who were MHS negative (MHN) on biopsy. The two groups were comparable with respect to height, weight and fat-free mass, calculated from body weight and skinfold thickness. There was no difference between the two groups in PWC_{150} (MHS: 1.37 ± 0.10 litre min^{-1}; MHN: 1.33 ± 0.20 litre min^{-1}; mean ± SEM; $\dot{V}\text{O}_2$ at STPD), in the slope and position of the heart rate–energy expenditure regression line nor in the calculated amount of work the subjects did at $\dot{V}\text{O}_2$ of 1.3 litre—that is, their efficiency (MHS 577 ± 26 kpm min^{-1}; MHN. 595 ± 25 kpm min^{-1}).

It is concluded that, as assessed using a discontinuous exercise test, there is no difference in work capacity between MHS and MHN individuals.

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MEASUREMENT OF TRUE TIDAL VOLUME DURING JET VENTILATION

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Measurement of tidal volumes and entrained volumes during high frequency jet ventilation is difficult using conventional techniques because of the high gas velocities and rapid changes in flow direction involved. A method which avoids these problems has been developed.

A diagram of the apparatus is shown in figure 3. A small microcomputer controls the jet ventilator via a solenoid valve. It is also fitted with a fast analogue to digital converter to log the flow signal from the screen pneumotachograph and the driving pressure signal. The pneumotachograph was chosen for its high frequency response and low thermal inertia. The monitoring of driving pressure is essential to avoid errors caused by delays of up to 65 ms in valve opening and closing after the electrical signal is applied and removed.

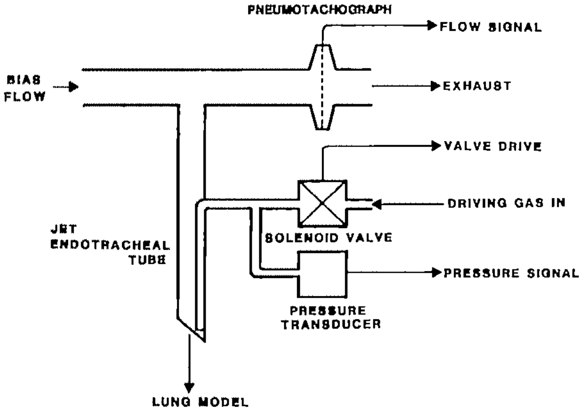

FIG. 3. Gas circuits.

During inspiration the jet entrains gas down the tracheal tube, causing a decrease in the flow measured by the pneumotachograph. The integral of this change is the entrained volume. During exhalation the flow signal increases, and the integral of this change is the sum of the volume delivered by the jet and the entrained volume. By simple mathematics the entrained, jet volume, tidal volume, mean driving pressure and true I:E ratio can be extracted.

The method is non-invasive, and requires only a constant bias flow; the actual value is not critical.

The system has been tested with a model lung consisting of a 52-litre closed container filled with metal wool to ensure isothermal expansion and compression. Pressure changes in the lung during ventilation were recorded. Using the known compliance of the lung, tidal volumes were cross checked and showed good agreement.

The method provides a simple, non-invasive method of calculating tidal volumes and entrainment ratios during jet ventilation which could be easily applied to animal or human studies.

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TOWARDS AUTOMATIC CONTROL OF GENERAL ANAESTHESIA

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The objective of this study was to investigate whether a simple feedback control system, driven by patient data and delivering an i.v. anaesthetic, could maintain general anaesthesia in fit patients undergoing general surgery. Systolic arterial pressure (SAP), which is one of the indices used by anaesthetists to assess the state of anaesthesia, was used as the controlled variable.

The study was approved by the local ethical committee. Twenty ASA I and II patients, aged 25–68 yr and undergoing routine general surgery, were studied. The patients were premedicated with temazepam, anaesthesia was induced with methohexitone and intubation facilitated with suxamethonium. The lungs were automatically inflated with 66% nitrous oxide in oxygen. Atracurium boluses were given as indicated by the response to nerve stimulation.

During surgery a Dinamap measured the SAP at 1-min intervals and passed the data to an RML microcomputer. The computer calculated a suitable infusion rate for a mixture of alfentanil 200 µg ml^{-1} and methohexitone 4 mg ml^{-1} in a fixed dose ratio which was then automatically delivered by an IP3 pump. A proportional plus integral algorithm with empirically determined gains (0.5 and 0.2, respectively) was used. The target SAP was the age/sex adjusted normal value less 10 mm Hg. The anaesthetic state and recovery were evaluated by appropriate scores (Asbury, 1981; Evans and Davis, 1984).

None of the patients gave evidence after operation of awareness during the operation. One anaesthetic was switched to manual control because the patient sweated and his SAP increased. Two patients were unable to give their date of birth by 15 min, and received naloxone. In the remaining 17 patients, anaesthesia was clinically satisfactory, with no patient having an anaesthesia score greater than 3; the mean alfentanil dose was 1.44 µg kg^{-1} min^{-1} (range 0.38–4.53); in recovery, patients gave their date of birth in a mean time of 5.3 min, and all had the top recovery score at 15 min; however, the quality of SAP control was variable.

Thus in most of our patients SAP contained enough information to allow the production of a satisfactory state of anaesthesia, which was associated with rapid awakening. Future developments will include the incorporation of other controlled variables and the improvement of the control algorithm.

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A SIMPLE METHOD FOR DETERMINING THE APPROPRIATE CORRECTION FOR TRANSIT AND RESPONSE TIMES OF A FAST RESPONSE ANALYSER

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The mixed expired concentration of a respired gas can be determined by analysis of a mixed expired sample, or by calculating from the integral of the product of the instantaneous expired flow and gas concentration signals. With the latter technique it is necessary to apply a time delay to the flow signal to compensate for the delay to the concentration signal resulting from the transit time of the gases along the sampling capillary, and the response time of the analyser itself. These two components may be measured separately, but Graham and colleagues (1985) have shown that, when a mass spectrometer is used in a multiplex mode (that is measuring several gases in a rapidly repeating sequence), a single delay time can be identified which applies to all dry gases. This delay applies only to a particular sampling capillary. In order to determine the appropriate delay we have assumed that, under steady state conditions, the calculated and measured mixed expired gas concentrations should be identical.

A model lung was fed with a constant flow of argon 250 ml min^{-1} and ventilated at a constant minute volume (8 litre min^{-1}) by a Nuffield 200 ventilator. Flow was measured with an Accutach pneumotachograph head and Validyne MP45 transducer situated between the ventilator and lung. The flow signal was then integrated digitally by a Research Machines 380Z microcomputer which was programmed to allow a variable delay to be added. The gas concentration was measured close to the pneumotachograph by a Centronics 200 MGA spectrometer, the output of which was fed to the microcomputer. The expired gases passed from the non-rebreathing valve of the ventilator through two mixing boxes and was sampled by the mass spectrometer.

By using a series of delay times 16 ms apart (the multiplex cycle time) it was possible to identify the delay (263 ms) which produced the minimum error (>2%) in calculated mixed expired concentration at three different deadspaces (100, 150, 200 ml).

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TABLE VIII. *Myoglobin* (*μg litre*$^{-1}$) *and creatinine kinase* (*iu litre*$^{-1}$) *concentrations* (*mean, SD*). *P < *0.01, Mann–Whitney*

	Minor surgery		Major surgery	
	Myoglobin	CK	Myoglobin	CK
Before ind.	22 (11)	40 (18)	37 (25)	49 (27)
Postop.	95*(84)	52 (25)	321*(211)	148*(120)
1st day	140*(92)	375*(424)	411*(329)	544*(312)
2nd day	75*(71)	354*(322)	178*(91)	545*(363)
3rd day	50 (50)	288*(236)	122*(98)	400*(333)

SERUM MYOGLOBIN AND CREATININE KINASE CONCENTRATIONS FOLLOWING SURGERY

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Suxamethonium administration results in an immediate increase in serum myoglobin concentration, which returns to near preinduction values within 24 h (Laurence, 1987). Enzyme profiles are often used to assist diagnosis of myocardial infarction, but in the postoperative period this may be more difficult because surgery can result in increased enzyme concentrations (Bendz and Strom, 1981).

The effect of muscle cutting surgery on postoperative serum myoglobin and total creatinine kinase (CK) concentrations was studied. Local ethical approval and patient informed consent were obtained. Suxamethonium was not used during anaesthesia.

Blood was drawn before induction, at the conclusion of surgery and on subsequent mornings until the 5th to 7th days after operation. Many samples were combined with routine postoperative care, but some needed additional venepunctures. All specimens were separated and frozen before assay for serum myoglobin by radioimmunoassay and CK, in batches.

A total of 30 patients have been studied. Patey mastectomy, abdominal operations with midline incision and subcostal cholecystectomy were classed as minor muscle cutting operations (15 patients). Major muscle cutting operations included total hip replacement, massive bilateral subcostal incisions and thoraco–abdominal operations (15 patients). No patient presented any clinical indications of perioperative myocardial infarction.

Mean serum myoglobin and CK concentrations are shown in table VIII, together with the statistical comparison against pre-induction data. Although not apparent from the mean figures, CK peaked 1 day later (day 1–2) than myoglobin (day 0–1) in individual patients. This difference in day of peak myoglobin and CK values was also statistically significant ($P < 0.02$ major; $P < 0.005$ minor, Mann–Whitney).

In the minor group, myoglobin and CK increases occurred even in patients without any muscle cutting at all. The smallest increases occurred after Patey mastectomy and midline cholecystectomy. In the major group the highest recorded serum myoglobin, 1390 μg litre^{-1}, occurred on day 1 following a thoraco–abdominal resection. The highest recorded CK was 1339 iu litre^{-1} occurring on day 2. Thus the magnitude and duration of these increases can be comparable to those following myocardial infarction.

ACKNOWLEDGEMENTS

We thank the University of Sheffield Research Fund for financial assistance, Mr P. Henderson for the radioimmunoassay and the Clinical Chemistry Department, Preston for CK estimations.

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COMPARISON OF FENTANYL AND SUFENTANIL ANAESTHESIA FOR PATIENTS UNDERGOING CORONARY ARTERY BYPASS GRAFTING

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Sufentanil, a synthetic opioid (Rosow, 1984), was compared with fentanyl for the induction and maintenance of anaesthesia until the time of sternotomy in patients undergoing coronary artery bypass grafting. Forty adults, all receiving β-blocking therapy, with moderate to good left ventricular function (ejection fraction > 40%) were premedicated with lorazepam 4–6 mg 2 h before operation.

Patients were preoxygenated for 5 min and baseline haemodynamic measurements were recorded. One minute before induction they received pancuronium 0.03 mg kg^{-1} and were randomly allocated to receive sufentanil 5 μg kg^{-1} or fentanyl 25 μg kg^{-1} i.v. via the central line over 1 min. Time to loss of eyelash reflex was noted and at this time pancuronium 0.07 mg kg^{-1} was administered. Haemodynamic measurements were made 5 min after the initial dose of pancuronium, the patient was intubated and further measurements were made 60 s after this. A supplementary dose of sufentanil 2.5 μg kg^{-1} or fentanyl 12.5 μg kg^{-1} was given 1 min before skin incision and also 1 min before sternotomy, haemodynamic measurements being recorded before and after both events. Patients were ventilated with 50% air–oxygen to maintain normocarbia. Measurements of haemodynamic performance were analysed using repeated measures analysis of variance.

The groups were broadly comparable with respect to age, weight, time to skin incision and time to sternotomy. Mean

TABLE IX. *Mean arterial pressure ± SEM (mm Hg). int. = Intubation; ster. = sternotomy*

	Base	5 min	Post-int.	Pre-skin	Post-skin	Pre-ster.	Post-ster.
Sufentanil	99±2.9	80±3.5	88±3.1	81±2.9	85±3.4	93±3.3	94±3.3
Fentanyl	101±3.3	90±3.0	98±3.0	96±3.2	98±3.2	102±2.7	104±3.7

times to loss of eyelash reflex were 67 s and 82 s from commencement of administration in the sufentanil and fentanyl groups, respectively (not significant).

Sufentanil produced a significantly greater decrease in mean arterial pressure following induction, which remained lower throughout the period of study than that in the fentanyl group ($P < 0.05$) (table IX).

Heart rate showed a slight but significant increase from the baseline values following induction and intubation in both groups, but returned to baseline values during the remainder of the study. Cardiac index remained stable during induction and intubation with a greater decrease before skin incision in the sufentanil group, although the difference did not reach significance. Mean pulmonary and capillary wedge pressures showed no significant change during the study in either group.

Sufentanil, in the doses used in this study, produced satisfactory induction of anaesthesia and a lower mean arterial pressure throughout the study than fentanyl.

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EFFECT OF POSITIVE END-EXPIRATORY PRESSURE ON EXTRADURAL PRESSURE

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The extradural pressure increases when a patient turns from the lateral to the supine posture (Shah, 1984). Increase in extradural pressure is probably caused by an increase in the volume and pressure of blood in the extradural veins. Positive end-expiratory pressure (PEEP) causes an increase in the vena cava pressure. As a result of the transmission of this venous pressure into the extradural veins, PEEP should also cause an increase in extradural pressure.

With ethical committee approval and patients' informed consent, the effect of PEEP on extradural pressure was studied in four patients aged 40–45 yr undergoing abdominal hysterectomy. The patients were anaesthetized and ventilated and extradural block was provided for intra- and postoperative analgesia.

At the conclusion of surgery and before the termination of anaesthesia, PEEP ranging from 5 to 20 cm H_2O was applied for approximately 30 s. Changes in the extradural pressure and airway pressures were measured using Hewlett–Packard pressure transducers and recorded on a multichannel tape recorder.

Application of PEEP produced an immediate increase in the extradural pressure. The increase in extradural pressure was related to the amount of PEEP applied, and differed in each patient (fig. 4). Withdrawal of PEEP produced an immediate return of extradural pressure to the pre-PEEP baseline values.

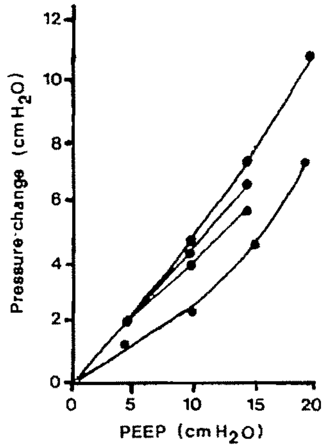

FIG. 4. Change in extradural pressure with increasing PEEP.

PEEP increases the central venous pressure. Transmission of this pressure to the extradural veins via the rich anastomosis between them, the vertebral veins, and the veins of the thoraco–abdominal cavity may be responsible for the increase in extradural pressure. Other possible mechanisms are the direct transmission of increased thoracic and abdominal pressure throught the intervertebral foramina, or transmission of increased cerebrospinal fluid (CSF) pressure into the extradural space. PEEP has been shown to increase the CSF pressure (Luce et al., 1982), and increased CSF pressure is transmitted into the extradural space (Shah, 1981).

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INVESTIGATION OF THE EFFECT OF PASSIVE HYPERVENTILATION ON SEIZURE DURATION IN PATIENTS HAVING ELECTROCONVULSIVE THERAPY

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It is known that hypocarbia during enflurane anaesthesia increases cerebral irritability (Neigh, Garman and Harp, 1971). Therefore the present study evaluated the effect of passive hyperventilation during electroconvulsive therapy (ECT) on seizure duration.

Thirty patients, aged 31–91 yr were randomly allocated to three separate ECT treatments. Local hospital ethical approval and verbal informed consent were obtained. Transcutaneous oxygen saturation was measured throughout anaesthesia and ECT. Patients were preoxygenated, breathing normally, until oxygen saturation reached 98%. Anaesthesia was then induced with methohexitone 1 mg kg^{-1} and suxamethonium 0.5 mg kg^{-1}. A different mode of ventilation was used before ECT on three occasions. No ventilation, 10 breaths or 20 breaths of oxygen was delivered via a non-rebreathing system with an Ambu valve and a fresh gas flow of at least 200 ml kg^{-1}. End-tidal carbon dioxide (FE_{CO_2}) was measured before the shock, and after the seizure, sampling through the face mask. A standard 3-s bilateral ECT current was used (Ectron Duopulse) and seizure duration was measured using the isolated forearm (Fink and Johnson, 1982). The results were analysed by linear regression, analysis of variance for correlated means and the Tukey test where appropriate.

Oxygen saturation did not decrease to less than 90% during any treatment. Mean (SEM) FE_{CO_2} was significantly different in the three groups before the shock ($P < 0.01$). Following the seizure, FE_{CO_2} was greater after no ventilation compared with 10 breaths ($P < 0.05$) and 20 breaths ($P < 0.01$). Fit duration was longer after 20 breaths compared with 0 or 10 breaths ($P < 0.01$) (table X). There was significant between subjects variation in seizure duration ($P < 0.01$). Seizure duration was not significantly correlated with FE_{CO_2} before ECT, or with change in FE_{CO_2} during the fit.

TABLE X. FE_{CO_2} *and seizure duration (mean, SEM) in the three groups*

	FE_{CO_2} before ECT (%)	FE_{CO_2} after fit (%)	Seizure duration (s)
No ventilation	4.95	5.80	30.3
	(0.10)	(0.16)	(2.2)
10 breaths	4.38	5.40	32.4
	(0.18)	(0.14)	(2.3)
20 breaths	3.86	5.25	36.8
	(0.18)	(0.15)	(2.0)

Therefore, passive hyperventilation prolonged induced seizure duration during ECT. Individual variation in seizure duration may explain the finding that FE_{CO_2} before ECT and seizure duration were not significantly correlated.

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PHARMACOKINETICS OF PROPOFOL DURING AND AFTER I.V. INFUSION IN MAN

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The pharmacokinetic profile of propofol (2,6-diisopropylphenol) in an emulsion formulation has been studied in normotensive patients undergoing body surface operations. All patients gave their informed consent. Patients were premedicated with morphine 0.15 mg kg^{-1} 1–2 h before surgery.

Anaesthesia was induced in all patients with propofol 2 mg kg^{-1} and maintained with propofol either 54 µg kg^{-1} min^{-1} (group I, $n = 8$) or 108 µg kg^{-1} min^{-1} (group II, $n = 8$); patients breathed 67% nitrous oxide in oxygen, with either spontaneous or controlled ventilation in sequence, during the infusion, which was continued for about 2 h in both groups.

Venous blood samples were taken during the infusion and up to 8 h following its termination; propofol concentrations were determined by an HPLC–fluorescence assay and curve fitting was performed using ELSFIT. Differences in pharmacokinetic parameters between treatment groups were assessed using the Wilcoxon Rank Sum Test.

Individual blood concentrations of propofol decreased slightly following the initial dose to reach a trough about 10–20 min after induction; thereafter concentrations increased gradually to approach the steady state value for the infusion rate being administered. Following the termination of the infusion concentrations decayed in a curvilinear manner with time.

The propofol blood concentration data were best fitted by a triexponential function and pharmacokinetic parameters were therefore determined assuming a three-compartment open mamillary model. Mean data are presented in table XI.

TABLE XI. *Pharmacokinetic parameters (mean ± SEM). *Approximate value only*

		Group I ($n = 8$)	Group II ($n = 8$)
$T_{\frac{1}{2}}^{\alpha}$	(min)*	3 ± 1.5	4 ± 1.5
$T_{\frac{1}{2}}^{\beta}$	(min)	29.7 ± 4.7	36.8 ± 6.8
$T_{\frac{1}{2}}^{\gamma}$	(min)	308 ± 47	511 ± 153
V^{γ}	(litre)	832 ± 116	996 ± 233
V^{ss}	(litre)	263 ± 34	319 ± 80
Cl	(litre min^{-1})	1.93 ± 0.15	1.54 ± 0.13
C^{ss}	(µg ml^{-1})	2.43 ± 0.20	4.75 ± 0.17

Propofol concentrations displayed only a shallow decline after the induction dose and the distribution phase after infusion was truncated as expected; thus $T_{\frac{1}{2}}^{\alpha}$ is only approximate and no accurate estimate for the initial distribution volume can be made.

There was no significant difference between treatment groups in mean half-life, volume of distribution or clearance values. These values are in good agreement with those observed following a single dose (2.5 mg kg^{-1}) to male or female patients (Kay et al., 1986). The mean steady state propofol blood concentration, predicted from the individual fitted models, increased linearly with infusion rate.

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METABOLIC EFFECTS OF DOPAMINE

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Dopamine is a precursor of adrenaline and noradrenaline and is frequently used pharmacologically. Adrenaline and noradrenaline have metabolic effects—increases in whole body oxygen consumption and stimulation of lipolysis and glycogenolysis (Jung et al., 1979; Fellows, Bennett and MacDonald, 1985). There are no data on the metabolic effects of dopamine.

Five male volunteers, median age 32 (range 29–40) yr, were each randomized for study on two separate occasions. They were fasted overnight and resting oxygen consumption measured for 30 min at rest and during infusion of dopamine 800 mg in 5% dextrose 500 ml or the corresponding volume of 5% dextrose alone, at doses of 2, 5 and 10 µg kg^{-1} min^{-1} for three consecutive 45-min periods with 5 min between each period when the infusion rate was increased gradually. Venous blood was taken at 30 and 45 min of each infusion period and analysed for lactate, glucose, free fatty acids, glycerol, sodium, potassium, noradrenaline, adrenaline and dopamine. Arterial pressure, heart rate and ECG were monitored.

Blood glucose increased during dopamine infusion and was significantly higher at 30 and 45 min of the 5-µg and 10-µg infusion ($P < 0.01$) than during dextrose only infusion. Free fatty acids and glycerol concentrations were greater at 30 and 45 min of the 10-µg infusion ($P < 0.05$), adrenaline at 30 min of the 2-µg infusion only ($P < 0.01$) and noradrenaline at 30 and 45 min of both the 5- ($P < 0.05$) and 10-µg ($P < 0.01$) infusions. Lactate did not alter in either group with no difference between the groups. Sodium did not alter in either group, but potassium decreased by 0.3 mmol $litre^{-1}$ ($P < 0.05$) during dopamine infusion.

Oxygen consumption increased by 6% with dextrose and by 20% with dopamine. Oxygen consumption was higher during dopamine infusion at 15–30 ($P < 0.01$) and 30–45 ($P < 0.05$) min of the 10-µg infusion than during dextrose infusion alone. Dopamine concentrations increased proportionately with the infusion rate to more than 1000 nmol $litre^{-1}$, but remained below 1 nmol $litre^{-1}$ when dextrose only was given.

It is concluded that dopamine has metabolic effects. It increases oxygen consumption and stimulates glycogenolysis and lipolysis. These effects could be a function of the dopamine dosage or of the duration of its administration. They could also be a direct effect of dopamine or a result of noradrenaline release.

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CORE TEMPERATURE CHANGES DURING ANAESTHESIA FOR VARICOSE VEIN SURGERY

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The occurrence of hypothermia during major abdominal, thoracic or vascular surgery is recognized. However, there are no data on core body temperature (CT) changes during superficial surgery for bilateral varicose veins. Approximately 40% of body surface area is exposed during this type of surgery. This study describes CT changes and the frequency of hypothermia (defined as CT < 35 °C) in patients undergoing surgery for bilateral varicose veins. In all patients anaesthesia was induced with thiopentone, supplemented with phenoperidine, neuromuscular blockade with alcuronium, and a tracheal tube and an oesophageal temperature probe were passed. Ventilation (IPPV) was with nitrous oxide 2 litre: oxygen 1 litre via a circle breathing system. Neuromuscular blockade was antagonized with a neostigmine–atropine mixture. A calibrated thermocouple thermometer was used to measure temperature of the lower one-quarter of the oesophagus. CT, heart rate, arterial pressure, ECG, end-tidal carbon dioxide concentrations, inspired gas temperature were monitored and recorded every 15 min. The ambient temperature was 22 °C±0.5. Patients were randomized into three groups. In group I ($n = 16$) no specific measure was taken to conserve heat. In group II ($n = 10$), a heat reflecting cover was placed around the canister of the circle sytem to conserve heat. Patients in group III ($n = 15$) were placed on a warm (36.5 °C±0.5) water ripple mattress. Mean CT decreased in all groups; however, the decrease in group I (2.3 °C, SEM±0.14) was significantly greater than that in groups II (1.9 °C±0.09) or III (1.2 °C±0.09) ($P < 0.01$). Furthermore,

TABLE XII. **Significantly greater than group II and III* (P < *0.05*)

	Group I	Group II	Group III
Mean duration of op. (h)	2.84 (1.54–4.0)	2.47 (1.55–4.3)	2.57 (2.05–4.5)
No patients			
Hypothermic	8 (50 %)*	2 (20 %)	0
Shivering	13 (81.25 %)*	4 (40 %)	3 (20 %)
With arrhythmias	6 (37.5 %)*	0 (0 %)	0 (0 %)

the frequency of hypothermia, shivering and arrhythmias in group I was significantly greater than in groups II or III ($P < 0.05$) (table XII). There is a real risk of hypothermia during anaesthesia for bilateral varicose vein surgery. This may be reduced by conventional methods of heat conservation during anaesthesia.

FUNCTIONAL STATUS OF PULMONARY ALVEOLAR MACROPHAGES FOLLOWING EXPOSURE TO TOXIC GASES

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Smoke inhalation injury is a major factor in fire victim mortality (Home Office, 1983). Modern synthetic materials burn to produce potent cellular poisons (HCN, CO). An *in vitro* study of the functional status of pulmonary alveolar macrophages (PAM) following smoke inhalation in humans was undertaken.

Fire victims ($n = 13$) with a significant smoke inhalation injury (history of smoke exposure and a corrected carboxyhaemoglobin > 10% (Clarke, Reid and Campbell, 1981)) were studied. Bronchoalveolar lavage (BAL) was undertaken following fibreoptic assessment on admission and at 4 and 24 h. Patients with 20% BSA burn alone ($n = 7$) underwent a single BAL. Controls ($n = 19$) were selected from outpatients attending for diagnostic bronchoscopy.

Lavage cell populations were characterized. PAM chemiluminesence and phagocytic capacity were measured and transmission EM was undertaken.

Total cell yield was significantly increased in the smoke inhalation patients at 4 and 24 h and the burns only patients compared with controls ($P < 0.05$). The 4- and 24-h samples from the smoke inhalation patients revealed increased numbers of immature PAM and a sub-group ($n = 6$) who mounted a significant polymorphonuclear response ($P < 0.05$). PAM-stimulated chemiluminescence was amplified in the 4- and 24-h samples from the smoke inhalation patients. PAM phagocytic capacity was not impaired in either group. EM demonstrated alterations in the membrane and intracellular structure of smoke-exposed PAM.

These results suggest that antibacterial functions of the PAM are not compromised following smoke exposure. There is evidence however of an expanded and "primed" population of PAM containing increased amounts of reactive oxygen species (OH^-, O_2, H_2O_2). This, together with EM evidence of a change towards an immature PAM population with increased membrane instability, may lead to the inappropriate discharge of free radicals and proteases following contact with the smoke. When combined with the capillary endothelial damage associated with a significant burn, the pathophysiological lesion implicated in ARDS could be produced. This may explain why patients who have suffered a significant inhalation injury (CO-Hb > 20%) combined with a burn (> 25% BSA) invariably go on to develop this clinical syndrome.

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CORRESPONDENCE

LUMBAR SYMPATHECTOMY: SPREAD OF RADIOPHARMACEUTICALS FOLLOWING A SINGLE-NEEDLE TECHNIQUE

Sir,—A single-needle technique for lumbar chemical sympathectomy, similar to that described by Hatangdi and Boas (1985), has been in use at this hospital for several years. The advantages over two or three-needle techniques include: less patient discomfort, quicker procedure, less radiation to the patient and operator, and reduced likelihood of needle trauma.

Although we have not encountered an increase in complication rate since introducing this technique, we have been concerned that the increased volume of 10% phenol used may spread further than intended.

Radiographic films 4 h after the procedure demonstrate that the radio-opaque contrast marker used to follow the spread of the phenol has been absorbed. Late spread of the injectate was, therefore, assessed using three radiopharmaceuticals: technetium 99 m (Tc99 m)-labelled albumin aggregates, (MAA) normally used in perfusion lung scans; Tc99 m-labelled colloid normally rapidly taken up by lymphatics, and transported to regional lymph nodes; Tc99 m pertechnetate normally rapidly distributed within the extracellular fluid compartment and concentrated in the thyroid.

After localizing the needle on the antero–lateral border of the 3rd lumbar vertebra and confirming optimum position with spread of Angiografin (65%) under image intensifier control, one of the radiopharmaceuticals was injected in a total of 1.3 ml of saline. Ten millilitre of 10% phenol in Conray 420 followed immediately over a period of 1–2 min.

Seven patients were investigated: three received MAA, two colloid and two pertechnetate.

After the MAA the nuclear medicine scintigram taken at 1 h was comparable to the radiographic film taken at the time of the procedure (fig. 1). An 18-h scintigram showed no change in distribution (fig. 2.).

The scintigrams after the labelled colloid showed no lymphatic uptake and remained localized as after the labelled albumin. Following the pertechnetate, rapid absorption occurred, with activity appearing in the thyroid at 1 h.

The initial distribution of 10% phenol as shown by image intensifier and immediate radiographs was matched by the distribution of particulate radiopharmaceuticals (MAA, colloid). Phenol may impair local lymphatic drainage, thereby inhibiting clearance of the colloid. Pertechnetate clearance from the injection site showed that qualitative extracellular fluid exchange was not impaired, and it is likely that low concentrations of phenol would have been detectable in serum.

As the 1-h and 18-h scintigrams were comparable to the initial radiographs, this may indicate that if initial placement is satisfactory the phenol remains in the vicinity of the sympathetic chain and is not widely disseminated.

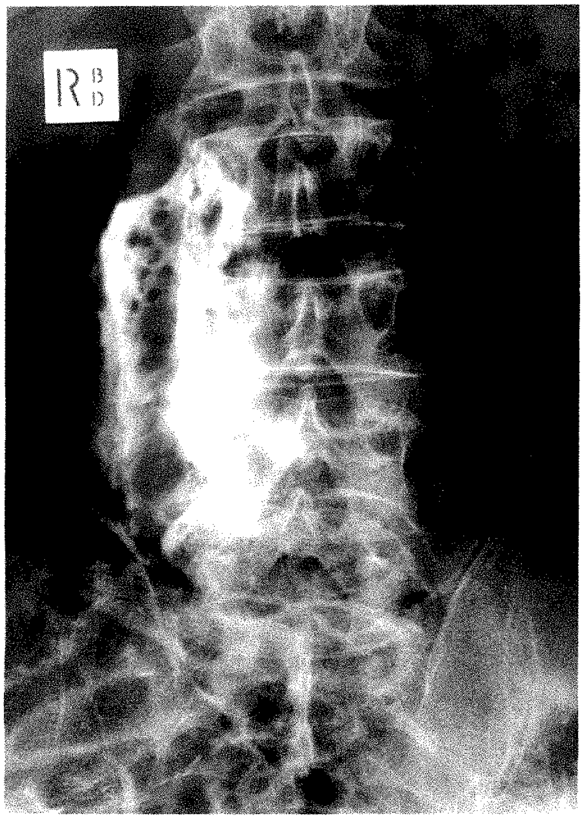

FIG. 1. Radiograph taken 15 min after the procedure.

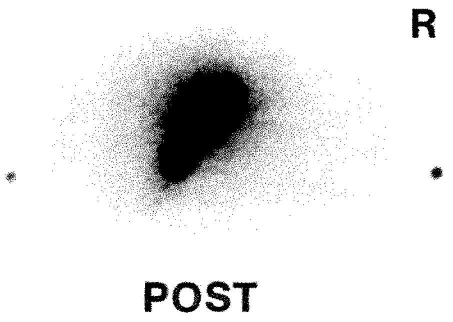

FIG. 2. Eighteen-hour scintigram following MAA. The markers indicate the position of the iliac crest; post = camera positioned posteriorly.

Further studies are planned to measure the serum concentrations of phenol following this technique and, as technetium 99 m does not label phenol directly, the spread of carbon-14 labelled phenol will also be investigated.

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BOOK REVIEWS

Parenteral and Enteral Nutrition, A Practical Guide (3rd Edn, 1986). By G. D. Phillips and C. L. Odgers. Published by Churchill Livingstone. Pp. 236; indexed; illustrated. Price £13.95.

This is the third edition of a monograph which evolved from notes written in 1977 as internal departmental guidelines on "Parenteral Nutrition and Gastric Tube Feeding". The first and second editions were published privately and their success led to the current commercial production. Since its modest beginning, the text has been expanded and key references added. Nevertheless, it was the authors' intention to maintain a concise didactic practical guide to a confusing subject. Have they succeeded? The current volume consists of 236 pages of text, 23 of appendices and 11 of comprehensive index. While marginally larger than pocket size, and clearly not a reference text, a considerable mass of information is contained therein.

The layout is fairly conventional, with introductory chapters on Background, Perspective, Logistics, Indications/Contraindications, Physiology of Nutrition, Pathophysiology and Biochemistry of Common Metabolic Disturbances. These are followed by discussions on Dietary Components, Nutritional Assessment, Monitoring and Complications. Later chapters are devoted to nutrition in certain disease states, Special Techniques, Paediatric Practice, Home Nutrition, and two excellent concluding contributions on Pharmaceutical Considerations and Responsibilities. Appendices 1–3 are concerned with equipment and No. 4 with pharmacological data, but No. 5 is a rather embarrassing homily entitled "Putting it all together—practically".

In general, the layout is clear and the text well illustrated with diagrams, although there seems to be a printing hiccup in the diagram of resting energy expenditure on page 37. At £13.95 this book could be an all-round winner. However, perhaps because "like Topsy—it growed" rather than was planned from the outset as a formal text, the book is more than usually uneven in chapter content. Some are unnecessarily detailed—metabolism merits 14 pages including five half-page biochemically-beloved maze-like diagrams, while nutrition in cardiorespiratory, hepatic and renal failure is dismissed in four. An unfortunate omission here was any mention of continuous arterio–venous haemofiltration and its relationship to the management of nutrition and fluid balance in this group of patients. Further criticisms must be of the irritating repetitions and occasional conflicting advice—particularly with regard to the now outdated references to metabolic requirements in critical illness. Additionally, many of the products discussed are not relevant to the British market and some which were have been superseded by newer formulations. Perhaps the next edition will see tighter control by the sub-editor over punctuation which would help to improve the fluidity of the prose. One's overall impression is that this could be an excellent guide but, in its present form, like the Curate's egg, only parts of it are excellent.

Winifred E. I. Finlay

Active Management of Labour, 2nd Edn. By K. O'Driscoll and D. Meagher, Published by Ballière Tindall. Pp. 204; indexed. Price £9.95.

The authors are well known advocates of active management in labour; their experience is drawn from working in a very busy maternity unit. This, the second edition, includes a new chapter on dilatation of the cervix and more detailed discussion on intrapartum fetal monitoring.

It is an easily read book aimed mainly at obstetricians and midwives, but is also of value to anaesthetists and physiotherapists working in modern day obstetrics. Each of its 27 chapters is short and to the point, with a summary at the end. The absence of anecdotes is a welcome change.

The book deals mainly with normal primagravid labours with vertex presentations and emphasizes the importance of this first birth experience. To their patients they give two assurances from the outset. First, that labour will last for less than 12 hours and, second, that the labouring mother will never be left alone—the psychological effects are never forgotten. These two guarantees, along with good antenatal preparation involving both medical and nursing staff, are emphasized throughout the book.

The crux of good management in the labour ward is the diagnosis of actual labour—often more difficult than first appreciated. If the progress in labour slows to below their accepted rate, oxytocin is administered. The danger of the use of this drug in parous patients is stressed.

The authors outline three major causes of abnormal labour: inefficient uterine action, cephalo–pelvic disproportion and occipito–posterior position. The early recognition and correction of the first are most important.

In the chapters relating to pain relief, they emphasize the role of psychological support. Narcotic analgesia, namely pethidine, is used within strict limitations for fear of side effects to the mother. Although extradural blockade is freely available, the rate of use is exceedingly low—in the region of 5 %. No prior commitment is made to the patient as to the use of this technique as this can lead to a negative attitude.

With their strict criteria for managing primagravid patients in labour, they have a spontaneous vaginal delivery rate approaching 90 %, with a remarkably low Caesarean section rate of 4.2 %. This latter rate is discussed in more detail in light of the increasing occurrence elsewhere in modern units.

Two sections at the end of the book show examples of the partographs of various problems in labour and the very satisfying improvement in the results of the authors' care over the past 20 years.

The National Maternity Hospital in Dublin is fortunate to have such co-operation between medical and nursing staff. There is one "Master" in charge of labour ward policy, with a sister midwife responsible for day-to-day running. I am sure these two facts are among the main reasons why the system outlined works so well for them.

J. H. Kennedy

Handbook of Neuroanaesthesia: Clinical and Physiologic Essentials. Edited by P. Newfield and J. E. Cottrell. Published (1983) by Little, Brown and Company, Boston. Pp. 437; indexed; illustrated. Price £18.85.

The 25 contributing authors of this text, which is intended to be read by neurosurgeons and anaesthetists, are all North American and are mainly neurosurgeons or anaesthetists, although there is one neuroradiologist and one otolaryngologist. The format of each of the 17 chapters varies considerably, ranging from a short note type of presentation to review article standard. Many of the chapters start with a discussion of basic neurophysiology and, consequently, there is much repetition of this material. Every chapter includes a useful list of references.

The book is divided into three sections. In the first section, which is entitled General Considerations, the physiology and metabolism of the brain and the effects of anaesthetic agents on these are discussed, electrical monitoring of the brain and spinal cord is described, and an excellent review of the cerebral metabolic properties of barbiturates is presented. Intensive Care—confined largely to respiratory care, cardiovascular therapy and fluid management—is the subject of the second section. The third section deals with the anaesthetic management of patients requiring neurosurgery or neuroradiological investigations and includes chapters on head and spinal cord trauma and paediatric neurosurgery.

Much of the material can be readily found in standard texts of anatomy, physiology and pharmacology, and it is difficult to know why the authors felt it necessary to revert to such fundamental knowledge to form the basis of their chapters. Some of the chapters are more a description of the authors' personal anaesthetic or investigative techniques, rather than a discussion of the methods available. Despite these criticisms, there is much of value and interest for neuroanaesthetists.

J. L. Jenkinson

Anaesthetic Management, A Rule-Based Guide. By M. J. Harrison, R. M. Jones and B. J. Pollard. Published by Butterworths. Pp. 281; indexed. Price £13.50.

The book *Anaesthetic Management* has been written by three authors, M. J. Harrison, R. M. Jones and B. J. Pollard, and it is always interesting to ponder which author has produced which part and, in particular, the excellent sections on diseases and anaesthesia.

The book had its origins in a computer program which was designed to advise the anaesthetist on the best techniques and drugs to use in various clinical situations. From this point of view it is interesting, as a clinician, to see how anaesthesia is interpreted by the logic of the computer. As computer logic is sequential, whereas clinical practice is more inclined to be that of lateral thought, the computer does appear to make heavy weather of what, to many clinicians, would appear to be obvious. The computer logic leads one to flow diagrams, which are in the earlier part of the book. These occupy a small part of the book and I would like to see an extension here as these diagrams are not only an aid to logical thought at the start of one's career, but would also be useful in revising for exam purposes later.

When a book is read it is interesting to consider at whom it is aimed. Certainly, as far as Part 3 of the F.F.A. is concerned, the book lacks sufficient depth and is not sufficiently specific concerning the doses of drugs. Consequently, one thinks of junior staff at the start of their career, but here I have reservations, as such situations as cardiopulmonary bypass for tracheal obstruction are discussed and, of course, the inexperienced should not be contemplating such cases. Befitting the suitability for junior staff and arising from the computer format, there is a dictatic approach to clinical problems. Most of us would, however, accept that there are several possible alternatives. Certainly, the reviewer disagrees with some of the comments and, from a personal point of view, is unhappy that, by and large, the solution to most situations is seen in general anaesthesia.

I admit to having found the book interesting, but this was mainly from the view of anaesthesia and the computer interface, rather than as a clinical text book.

J. Bowes

Cardiotonic Drugs. A Clinical Survey. Edited by C. V. Leier. Published by Marcel Dekker, Inc. Pp. 312

This book is the 7th volume in a series on Basic and Clinical Cardiology. It comprises seven chapters, written by different contributors, all of whom are cardiologists, with the exception of one pharmacologist. The majority are members of the staff of the Ohio State University College of Medicine.

The style of each contribution is that of a review article, with a large element of referencing to the literature. One chapter is devoted to two drugs, bipyridine derivatives, which are not available in the U.K. market. Another chapter concerned with the use of phosphodiesterase inhibitors concentrates mainly on studies with enoximone, which also is not available in the U.K market.

There is relatively little in this book to interest the majority of anaesthetists, apart from a detailed account of the measurement of myocardial inotropy, and an interesting chapter on digitalis. However, there may be material appropriate to those anaesthetists actively involved in research. In general, however, the book cannot be recommended for an anaesthetic departmental library.

On an editorial note, it is disappointing to see lack of standardization of figures or units.

G Smith

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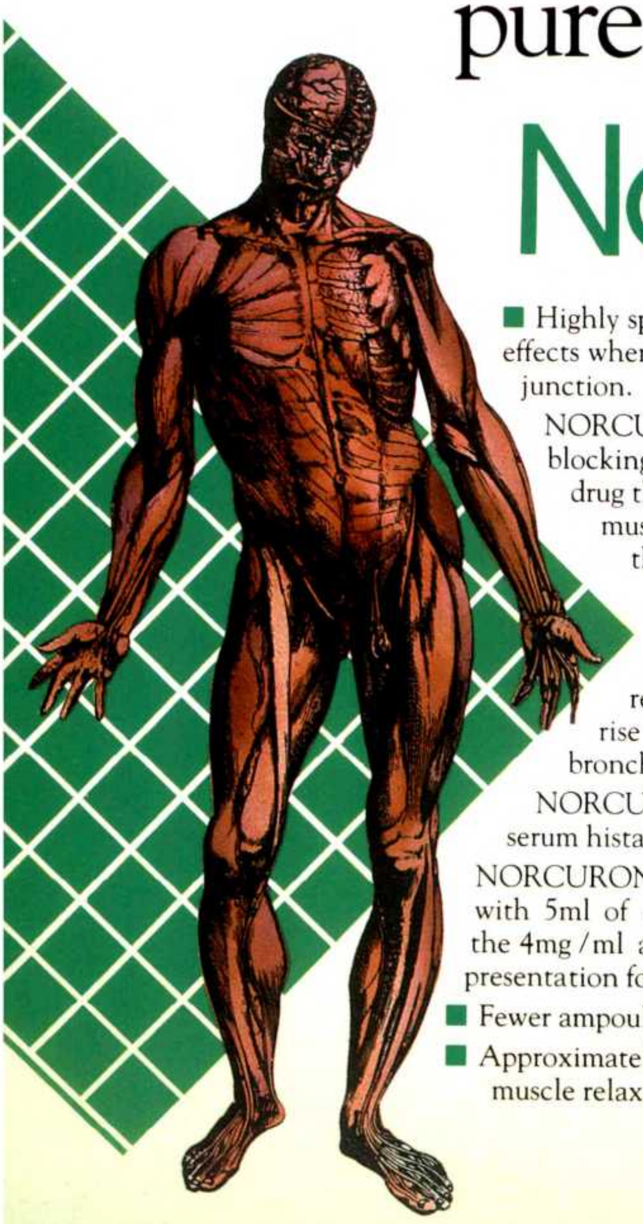

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1. Feldman SA; Clinical Experiences with Norcuron, Excerpta Medica (1983) 199-200
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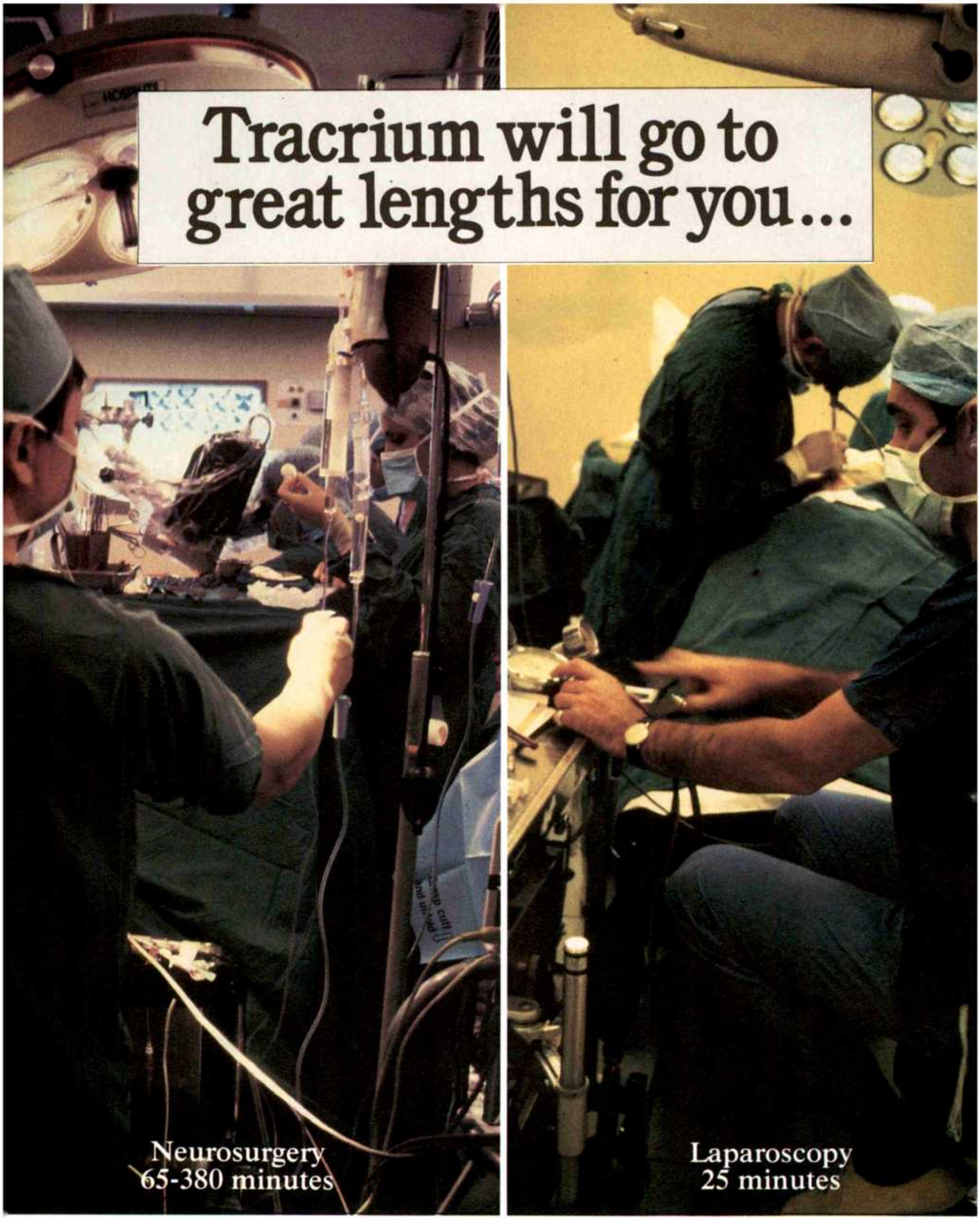

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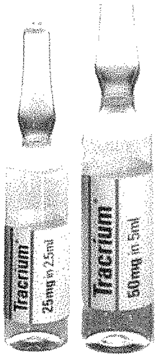

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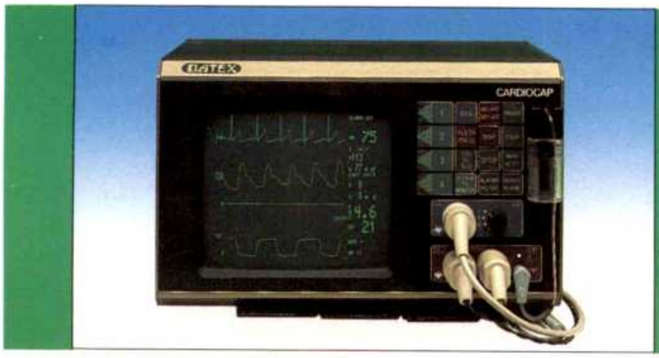

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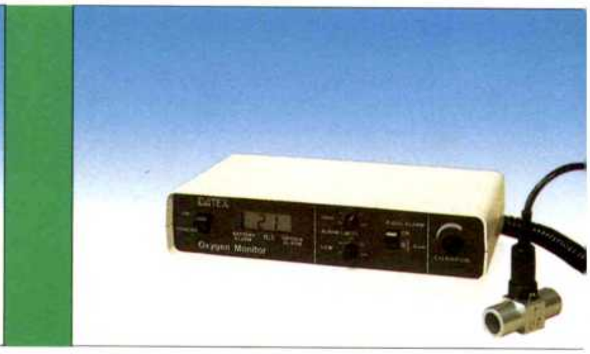

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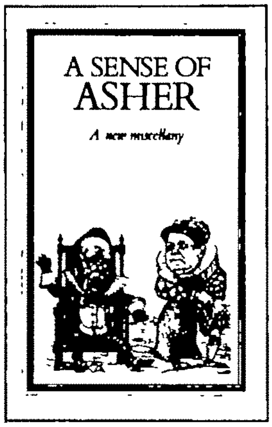

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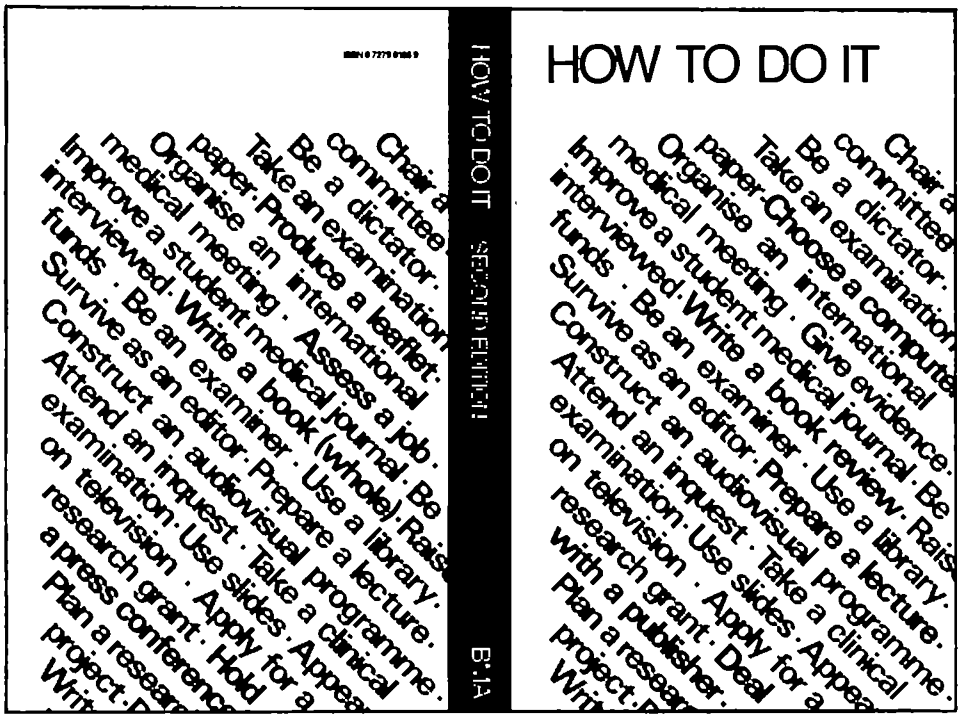

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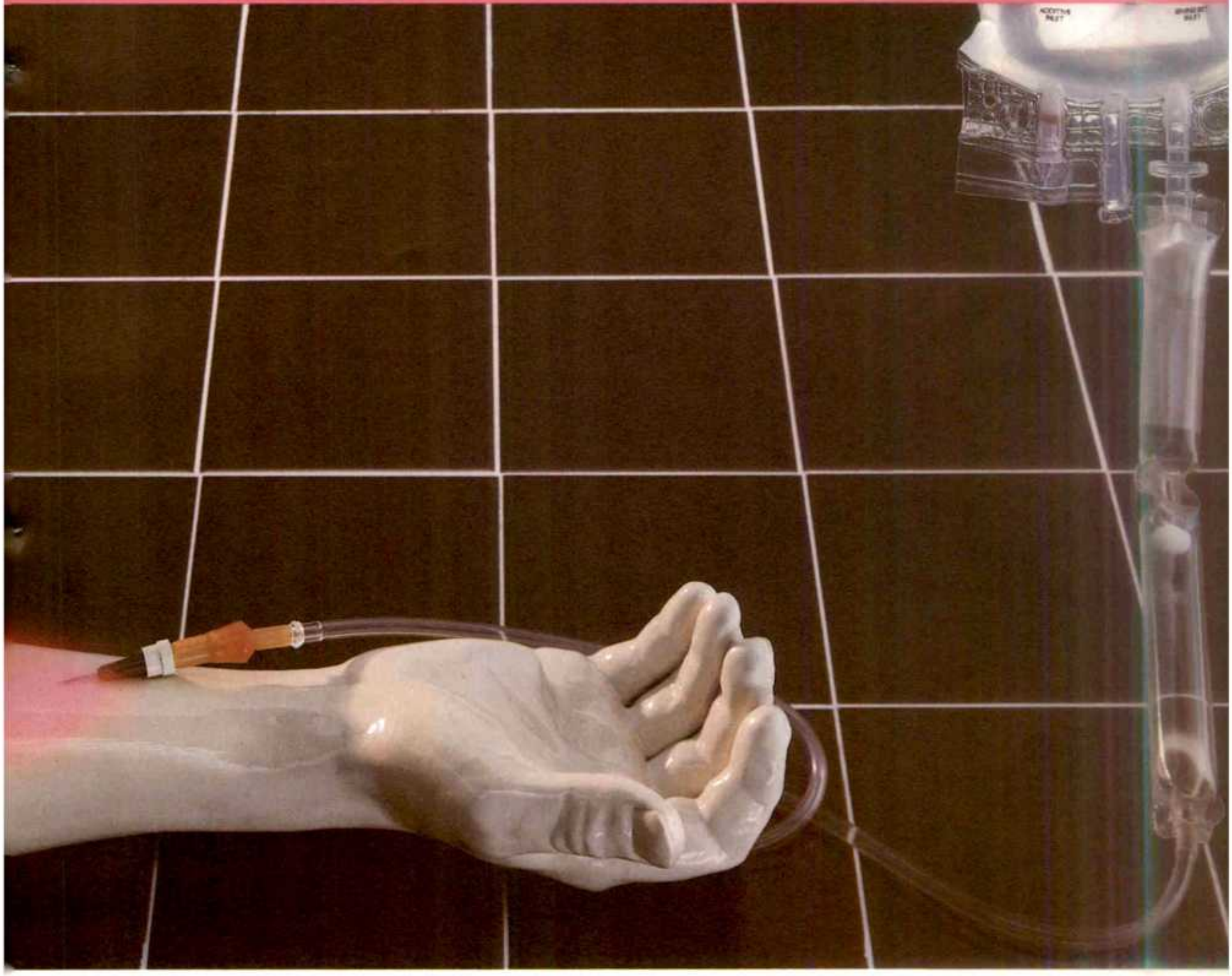

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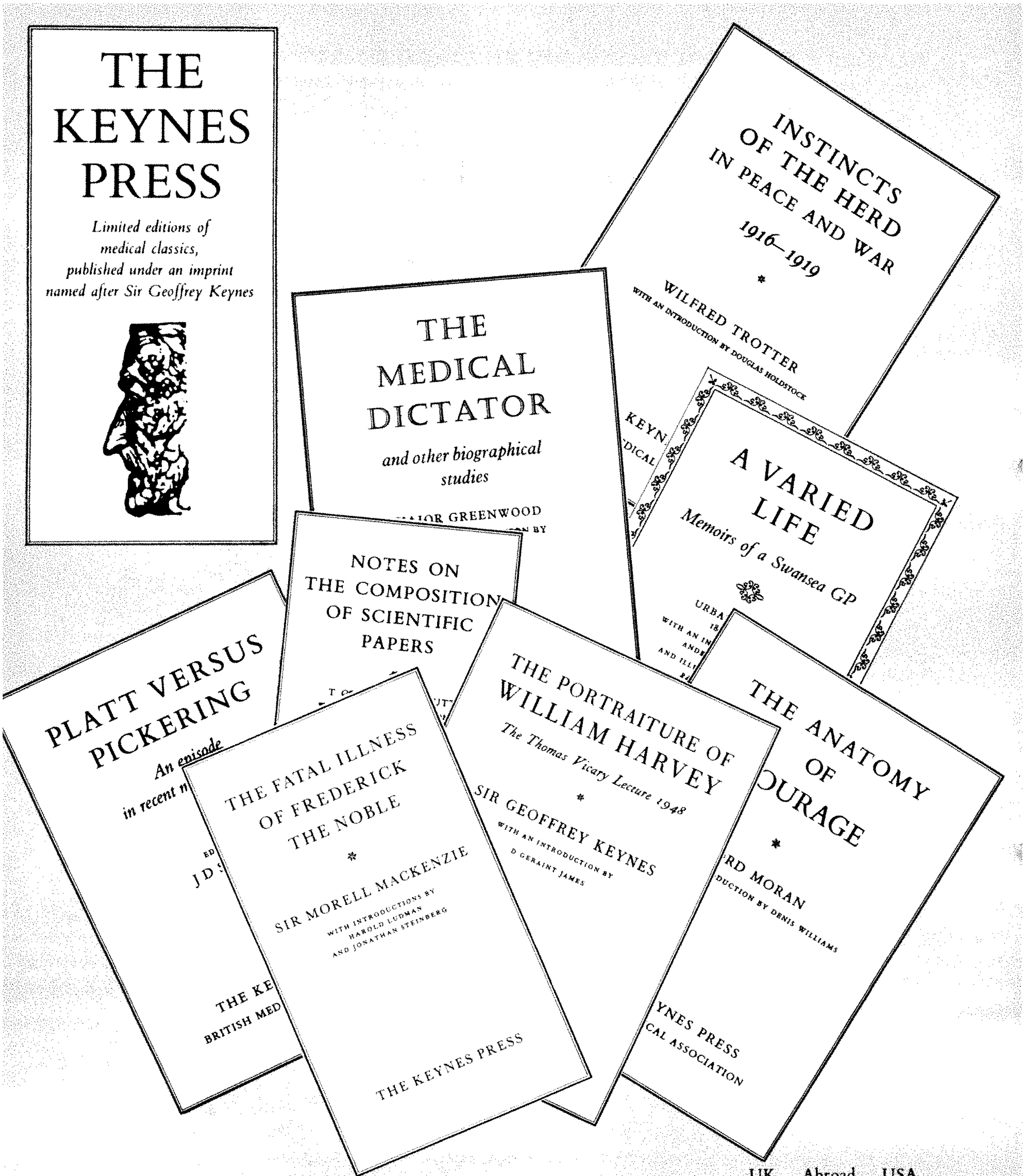
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EDITORIAL

ANAESTHESIA, AND ATELECTASIS: THE ROLE OF V_{TAB} AND THE CHEST WALL

An editorial written 10 years ago (Jones, 1977) postulated that the abnormality of gas exchange associated with anaesthesia was the result of decreases in the tone and movement of the chest wall which, together with an increase in thoracoabdominal blood volume (V_{TAB}), contributed to the decrease in functional residual capacity (FRC). The waning of support for the hypothesis of closing volume—as a cause of the gas exchange abnormality during anaesthesia—left considerable uncertainty about the causal relationship between a decrease in FRC and the increased abnormality of gas exchange (Rehder et al., 1977). Despite the fact that a reduction in lung volume during anaesthesia is associated with an increased abnormality of gas exchange, increasing lung volume does not reverse this abnormality (Heneghan, Bergman and Jones, 1984). On this basis, is a reduction in lung volume relevant to impaired gas exchange during anaesthesia, or is it a coincidental finding?

This editorial reviews some of the evidence that changes in the tone and movement of the chest wall following the induction of anaesthesia have an effect on lung volume; that an increase in thoracoabdominal blood volume is an important cause of the reduction in FRC; and that the reduction in FRC is associated with atelectasis in the dependent lung, which explains the impairment of gas exchange.

Little information was available about the effect of anaesthesia on diaphragm tone in man until Muller and colleagues (1979) measured the EMG as an index of tone in the diaphragm. During halothane anaesthesia they showed a significant reduction in diaphragm tone and postulated that this caused the reduction in FRC during anaesthesia. This mechanism supported the widely quoted report of Froese and Bryan (1974) that there was a cephalad shift of the diaphragm during general anaesthesia. The tone of the intercostal muscles is even more sensitive than that of the diaphragm to the depressant effects of volatile anaesthetics (Jones, 1977). This would suggest that anaesthesia, by reducing the tone of the diaphragm and intercostals, causes a reduction of lung volume as a result of an inward movement of the chest wall. However, it would not be expected that the reduction of muscle tone with general anaesthesia would, by itself, be as great as that when combined with neuromuscular blockade. A surprising finding, therefore, has been the similarity, both in terms of a reduction of FRC and worsening of gas exchange, of the effects of general anaesthesia compared with combined anaesthesia with neuromuscular blockade (Hewlett et al., 1974a, b). Is there some other explanation for the similar effects of two quite different anaesthetic techniques on FRC?

An attempt to partition the reduction of FRC during halothane anaesthesia into rib cage and diaphragm components (Jones et al., 1979) led to the surprising finding that no change occurred in end-expiratory position of either rib cage or abdomen, and it was postulated that any reduction of FRC must be caused by an increase in thoracoabdominal blood volume (V_{TAB}). Other workers also found little or no change in chest wall volume when blood moved in or out of the thoracoabdominal cavity (Vellody et al., 1978; Hedenstierna, Lofstrom and Lundh, 1981; Kimball et al., 1985). However, Sjostrand (1952) had shown that, following the release of blood trapped in the legs by tourniquets, there was an increase in chest wall volume (V_{CW}) and a decrease in lung volume (V_{L}). Theoretically, if there is an increase in V_{TAB} then it would be expected that a reduction in lung volume or an increase in chest wall volume, or both, might ensue. These changes are summarized as follows:

$$\Delta V_{TAB} = -\Delta V_L + \Delta V_{RC} + \Delta V_{AB}$$

where the chest wall volume is the sum of rib cage volume (V_{RC}) and abdominal volume (V_{AB}). From the compliance of each of the three components it would be expected that an increase in V_{TAB} of 1 litre would decrease V_L by 600 ml and increase V_{CW} by 400 ml. However, Gilroy and co-workers (1985) showed that the actual changes in V_L and C_W were the reverse of those predicted. Kimball, Kelly and Mead (1986) produced an acute increase in V_{TAB} by inflating leg splints and showed similar changes with protection of lung volume. However, these changes are the opposite of those seen during anaesthesia where lung volume is not well protected. A partial explanation was proposed by Kimball, Kelly and Mead (1986) who noticed that, if the increase in V_{TAB} was maintained, there was a gradual reduction in the volume of the chest wall to control values, as a result of changes in chest wall muscle tone (Freund, Roos and Dodd, 1964; Muller et al., 1979), increase in lung recoil (Gelb, Southorn and Rehder, 1981), or airway closure (Jones, 1982); these may be the factors that explain the different effects of anaesthesia on the maintenance of lung volume.

That muscle tone is probably of particular importance was suggested by Mankikian and associates (1986) who showed that ketamine anaesthesia was associated with an *increase* in RC movement (as did Morel, Forster and Gemperle (1986)), no change in lung volume, but an increase in chest wall volume—which implies that lung volume was maintained by increasing chest wall volume. Bickler, Dueck and Prutow (1987), using methohexitone anaesthesia, showed no impairment of RC movement and no change in FRC with mask breathing, but a significant reduction in FRC following intubation and coughing.

More sophisticated techniques are now available for determining the relative contribution of ΔV_{TAB}, ΔV_{RC} and ΔV_{AB} (diaphragm) to changes in FRC during anaesthesia (Krayer et al., 1987). Dynamic spatial reconstruction of the thorax is achieved before and during anaesthesia using high speed x-ray computed tomography. The internal volume of the thorax is derived and the difference between thoracic volume and FRC gives tissue volume, the latter including blood volume. Anaesthesia with neuromuscular blockade reduced FRC by about 600 ml, but increased thoracic blood volume 300 ml. This contrasts with the findings of Hedenstierna and co-workers (1985) who found a reduction of thoracic blood volume of about 300 ml, but an increase in abdominal blood volume of 400 ml. Krayer and colleagues (1987) showed large individual differences in the effects of anaesthesia on ΔV_{RC} and ΔV_{AB} in their subjects, although the most consistent change was a reduction of V_{RC}. A cephalad volume shift of the diaphragm occurred in only four of eight subjects, which conflicted with the predictions of Froese and Bryan (1974).

Logan and co-workers (1987) have used stereogrammetric analysis to examine changes in the chest wall before and during thiopentone anaesthesia. Trunk volume increased in four and decreased in three subjects. There was no consistent increase or decrease in the rib cage or abdominal components, although patients with greater than normal weight tended to show a reduction in RC volume and the opposite change occurred in those with less than predicted weight. A larger reduction in lung volume during anaesthesia in obese patients was also reported by Lehane, Jordan and Jones (1980).

These results suggest that anaesthesia with volatile agents, with or without neuromuscular blockade, reduces FRC by increasing V_{TAB} with a variable effect on the rib cage and diaphragm because of reduced ventilatory muscle tone. Anaesthesia with ketamine or methohexitone may preserve the tone of the chest wall musculature and protect against a change in FRC following any change in V_{TAB}.

Thus a change in V_{TAB} is a determinant of FRC during anaesthesia and in anaesthetized, paralysed, ventilated patients the addition of halothane or enflurane caused an increase in lung volume in some subjects (Lehane, Jordan and Jones, 1980). Watney, Jordan and Hall (1987), in this issue, used a similar technique in ponies and showed that different volatile anaesthetics may have different effects on lung volume which may be attributable to effects on vascular capacitance. The major blood reservoir of the body lies in the abdominal vascular bed more than the limb vessels, and this can take up or release, actively and passively, the major part of any change in circulatory blood volume (Hainsworth, 1984). In contrast, the pulmonary blood volume may change by little more than 300 ml in man, the change occurring passively as a consequence of changes in extrapulmonary vascular beds. Studies of the effects of anaesthetic agents on splanchnic vasculature have been reported (Henriksson et al., 1985), and others reviewed by Arndt (1986), but detailed information on the effects of different anaesthetics on splanchnic capacitance in man is incomplete. The technique described by Lehane, Jordan and Jones (1980) and Watney, Jordan and Hall (1987) provides one approach to this problem which is relevant to the major fluid shifts taking place in anaesthesia, but which are largely uninvestigated.

This leaves for discussion the mechanism whereby a reduction in FRC causes an impairment of gas exchange. The forced airflow oscillation method for measuring airway resistance produces a graphic demonstration of the progressive reduction in airway calibre with diminishing lung volume (Jones et al., 1987) and raises the question of the likelihood of atelectasis during anaesthesia. Atelectasis while breathing at low lung volume was first demonstrated in fighter pilots exposed to high acceleration forces (Green and Burgess, 1962), and the first demonstration of impaired gas exchange when breathing at low lung volume was by Nunn, Bergman and Coleman (1965). Until recently, however, there was no direct evidence that the reduction of FRC during anaesthesia caused atelectasis. It had been assumed that the mechanism causing an abnormal gas exchange was a reduction in lung volume below the closing volume point of dependent airways. Heneghan, Bergman and Jones (1984) were unable to reverse the abnormal gas exchange induced by anaesthesia by increasing the FRC to preoperative values and postulated that collapse of the dependent lung had occurred, but that passive distension of the lung would be insufficient to expand the collapsed units. Subsequently, they showed that, when the same increase in lung volume was achieved in two ways, either by application of PEEP, or by phrenic nerve stimulation, the latter manoeuvre, by producing a greater degree of movement of the dependent part of the diaphragm, produced a significantly greater improvement in gas exchange (Heneghan and Jones, 1985).

However, the definitive proof of atelectasis occurring during anaesthesia was obtained using CT scanning of the lungs of anaesthetized patients and was presented by Hedenstierna and colleagues (Brismar et al., 1985; Hedenstierna et al., 1986; Tokics et al., 1987) in a series of brilliant papers which demonstrated the following:

(1) Dependent lung atelectasis developing during anaesthesia.

(2) The gas exchange abnormality could be explained entirely by the magnitude of atelectasis.

(3) Atelectasis persisted into the postoperative period, in some patients for at least 24 h.

(4) Atelectasis was only partially reversed by lung inflation.

A correlation between the magnitude of anatomical shunt and degree of lung collapse has previously been described in spontaneous pneumothorax (Norris, Jones and Bishop, 1968). It might be expected that active pulmonary vasoconstriction would reduce the magnitude of the gas exchange abnormality in man (Norris, Jones and Bishop, 1968); however, this effect may only partially compensate for reduced ventilation or be reduced by the concomitant administration of anaesthetics (Benumoff, 1986).

Atelectasis in the dependent lung during anaesthesia appears to be ubiquitous. Are there techniques which can reduce this effect? It has been shown clearly that adding nitrogen to the inspired gas during anaesthesia reduces the magnitude of atelectasis (Browne et al., 1970), but no apparent benefit on gas exchange has been demonstrated (Webb and Nunn, 1967). However, in the majority of patients the effect of atelectasis on Pa_{O_2} appears to be relatively small and may have a greater significance for postoperative oxygenation rather than during anaesthesia itself (Jones et al., 1985). Nevertheless, it is standard anaesthetic practice, certainly in the U.K., to administer at least 30% oxygen to counter this effect. The development and increasing application of pulsed oxygen saturation monitoring during anaesthesia suggests that the advantages of the routine administration of 30% oxygen may not provide as great a margin of safety as that obtained by breathing 21% oxygen, but with continuous monitoring of oxygen saturation. In this way impaired oxygen saturation can be immediately detected, underlying causes identified and appropriate treatment instituted. Is it only a matter of cost which prevents such a simple but essential device from being used to monitor every general anaesthetic?

J. G. Jones

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HAEMODYNAMIC EFFECTS OF A PROLONGED INFUSION OF PROPOFOL AS A SUPPLEMENT TO NITROUS OXIDE ANAESTHESIA †

Studies in Association with Peripheral Arterial Surgery

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AND K. SPELINA

SUMMARY

The haemodynamic effects of propofol at two infusion rates (54–65 and 108–130 $\mu g\ kg^{-1}\ min^{-1}$) have been studied during peripheral arterial surgery in eight elderly patients premedicated with morphine sulphate 0.15 $mg\ kg^{-1}$. The haemodynamic response to laryngoscopy and intubation was partially suppressed: neither arterial pressure nor heart rate exceeded awake values. During stable anaesthesia at the lower infusion rate before surgery, systolic (SAP) and diastolic (DAP) arterial pressures were significantly decreased from awake values (SAP: −47%; DAP: −46%) as a result of decreases in cardiac output (−32%) and systemic vascular resistance (SVR) (−9%). During surgery, with either spontaneous (SV) or intermittent positive pressure (IPPV) ventilation, both infusion rates were associated with decreases in arterial pressures when compared with the awake state. Cardiac output was decreased (SV: −35%, IPPV: −36%) and SVR increased (SV: +22%, IPPV: +45%) at the lower infusion rate; similar changes were observed during the faster infusion rate.

In its original formulation in Cremophor EL, 2,6-diisopropylphenol proved suitable for use as a continuous infusion to supplement nitrous oxide anaesthesia (Prys-Roberts, Davies et al., 1983). 2,6-Diisopropyl phenol has now been reformulated as an aqueous emulsion (propofol) (Stark et al., 1985) and has been extensively re-evaluated as an induction agent (Cummings et al., 1984; Rolly et al., 1985) and as a maintenance anaesthetic (Kay et al., 1985). We have shown that the minimum infusion rate (MIR) required to ablate the response to surgery in 50% of patients was not significantly higher than for the Cremphor EL formulation. Using probit analysis the ED_{50} for the reformulated solution (Coates et al., 1985) was found to be 54 (95% confidence limits: 43–62) $\mu g\ kg^{-1}\ min^{-1}$, and the ED_{95} was 91 (95% confidence limits: 75–191) $\mu g\ kg^{-1}\ min^{-1}$, when propofol was infused continuously to supplement 67% nitrous oxide anaesthesia in patients premedicated with morphine sulphate 0.15 $mg\ kg^{-1}$.

We have previously reported the dose-related haemodynamic effects of Althesin (Sear and Prys-Roberts, 1979a), minaxolone (Sear et al., 1981), methohexitone (Prys-Roberts, Sear et al., 1983) and both the old (Prys-Roberts, Davies et al., 1983) and new (Coates et al., 1987) formulations of 2,6-diisopropyl phenol. As an extension of this series of studies we describe the haemodynamic response of elderly patients to the induction of anaesthesia using propofol, and to the maintenance of prolonged anaesthesia using two infusion rates of propofol with 67% nitrous oxide during surgery with either spontaneous or controlled ventilation.

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PATIENTS AND METHODS

The study was approved by the Bristol Health District Ethics Committee and by the Committee on Safety of Medicines. Eight patients who required lower limb arterial surgery gave consent following a full detailed explanation of the proposed procedures. The five males and three females were aged between 56 and 70 yr (mean 65 yr) and weighed 52–90 kg. The selection criteria for the study excluded those with myocardial or neurological disease, insulin-dependent diabetes or impaired liver function and those receiving drugs for the treatment of cardiac disease.

All patients were premedicated with morphine sulphate 0.15 mg kg^{-1} i.m. 1 h before the start of the study. Under local anaesthesia, brachial artery, central venous (CVP) and two peripheral venous cathethers were placed. One venous catheter was used solely for the infusion of propofol—which was delivered from a calibrated Vickers IP3 infusion pump. The other was used for drug and fluid administration. The arterial and CVP catheters were connected to Gould–Statham P23Ia transducers and a Hewlett–Packard 78205 system. The electrocardiogram was recorded using the CM5 lead configuration. Cardiac output (CO) was measured intermittently using the indocyanine green dilution method; stroke volume (SV) and systemic vascular resistance (SVR) were derived by standard formulae and standardized to 70 kg body weight. After each estimation of cardiac output an arterial blood sample was taken for the analysis, with temperature correction, of $P\text{o}_2$, $P\text{co}_2$ and pH (ABL3 Radiometer) and, in six patients, for the later estimation of whole blood propofol concentrations by HPLC with fluorescence detection by a modification of the method previously described (Adams et al., 1981). To allow comparison with previous studies (Sear et al., 1981; Prys-Roberts, Davies et al., 1983; Prys-Roberts, Sear et al., 1983; Coates et al., 1987) a specific longitudinal programme was followed to allow within-patient measurements of haemodynamic responses to spontaneous ventilation before surgery, and to spontaneous and controlled ventilation during surgery at two stable blood concentrations of propofol. Two nominal infusion rates of propofol were used: IR_1 (54 μg kg^{-1} min^{-1}) and IR_2 (108 μg kg^{-1} min^{-1}) to obtain the differing blood concentrations. Retrospective measurement of the volumes actually infused indicated that the infusion rates were respectively 60 (IR_1) and 120 μg kg^{-1} min^{-1} (IR_2) in two patients, and 65 and 130 μg kg^{-1} in one patient.

TABLE I. *Programme for within-patient comparisons of spontaneous and controlled ventilation at two infusion rates. IR_1 = 54–65 μg kg^{-1} min^{-1}; IR_2 = 108–130 μg kg^{-1} min^{-1}; SV = spontaneous ventilation; CV = controlled ventilation*

	Awake	Anaesthesia				
Stage:	1	2	3	4	5	6
Ventilation	SV	SV	SV	SV	CV	CV
Propofol infusion (IR)	0	1	1	2	2	1

The sequence of events specifying the changes in ventilation and infusion rate and the onset of surgical stimulation are displayed in table I.

Propofol was administered as a 1% w/v aqueous emulsion containing 10% w/v soy bean oil, 1.2% w/v egg phosphatide and 2.25% w/v glycerol. Baseline haemodynamic measurements (stage 1) were recorded before the induction of anaesthesia with a single dose of propofol 2 mg kg^{-1} given over 20 s; the infusion of propofol (IR_1) was then immediately started. The heart rate and arterial and venous pressures were continuously recorded for 3 min after induction, at which time another set of haemodynamic measurements was recorded. The patients breathed 67% nitrous oxide and oxygen spontaneously from a mask and Mapleson A system until the 9th minute after induction, when suxamethonium 1 mg kg^{-1} was given to facilitate tracheal intubation. The vocal cords were sprayed with 4% lignocaine and controlled ventilation performed until the return of spontaneous ventilation. Immediately before the initial surgical incision, and not less than 30 min after induction, a further set of haemodynamic measurements was recorded (stage 2), followed by another set after 15 min of continued surgery (stage 3). One patient moved in response to the initial surgical incision, so surgery was temporarily stopped and the haemodynamic measurements recorded after a 5-min delay. Another patient moved at one moment during continuous surgery, and a single increment of propofol 20 mg was given to allow surgery to proceed. After the stage 3 measurements were completed, the infusion rate was increased to IR_2, no further movements occurred in response to surgical stimulation.

As ventilation was not overtly depressed following the increased infusion rate, a further set of haemodynamic measurements was made after waiting 30 min (stage 4). Intermittent positive pressure ventilation (IPPV) was established using an Oxford–Penlon ventilator incorporated to a circle breathing system without a carbon dioxide absorber; neuromuscular blockade was not required. Fresh gas flow was adjusted to maintain the end-tidal carbon dioxide within the range 5.2–5.5 kPa. To allow the cardiovascular system to stabilize in response to IPPV the next set of haemodynamic measurements was recorded 30 min later (stage 5). After this, the infusion rate was decreased to the previous rate (IR_1) and the final set of haemodynamic measurements recorded 30 min later (stage 6).

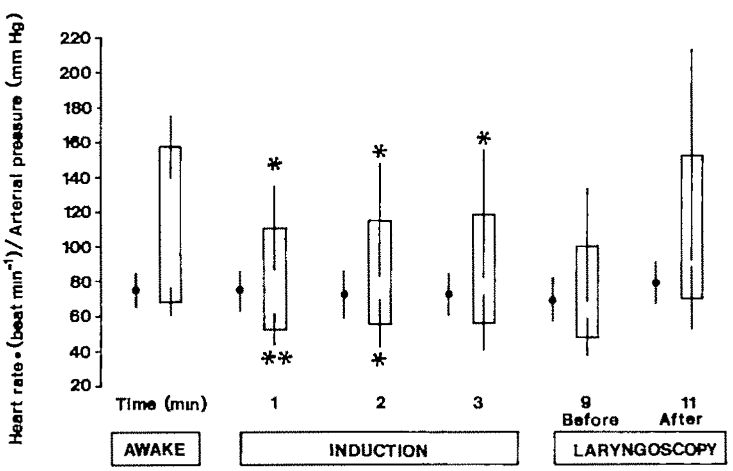
Anaesthesia was maintained with propofol and nitrous oxide until the completion of surgery when spontaneous ventilation was re-established. The trachea was exubated and the administration of nitrous oxide and propofol discontinued simultaneously. The times from stopping the infusion of propofol to the patient's response to command and the correct recall of birthdate were noted. All patients were interviewed the next day; and morbidity associated with the infusion of propofol was noted.

Statistics

The statistical analysis of the haemodynamic measurements was performed using repeated measures analysis of variance (ANOVA), and paired two-tailed Student's *t* tests with a correction factor for the Bonferroni inequality (Glantz, 1981).

RESULTS

The baseline haemodynamic measurements in this older patient population (stage 1) were comparable to those found in previous studies (Sear and Prys-Roberts, 1979a; Sear et al., 1981; Prys-Roberts, Davies et al., 1983; Prys-Roberts, Sear et al., 1983; Coates et al., 1987). The induction of anaesthesia with propofol was successful in the eight patients studied, all of whom became transiently apnoeic (range 45–105 s) and required transient manual ventilation. In the first 1 min after induction, significant decreases were observed in systolic (−29%) ($P < 0.05$) and diastolic (−22%) ($P < 0.01$) arterial pressures; heart rate remained unchanged (fig. 1). There were small, insignificant increases in systolic and diastolic arterial pressures in the 2nd and 3rd minutes. These changes on induction were accompanied by decreases in cardiac output (−13%), stroke



Cardiac output (litre min⁻¹/70 kg)	5.3 ± 0.9	4.8 ± 1.1
Stroke volume (ml/70 kg)	76 ± 17	68 ± 10
SVR (dyn s cm⁻⁵)	1393 ± 303	1310 ± 427
Pa_{CO_2} (kPa)	5.2 ± 0.4	6.0 ± 0.4*

FIG. 1. Haemodynamic responses (mean ± SD) to induction of anaesthesia with propofol and to subsequent laryngoscopy and endotracheal intubation. Time = time after induction. Compared with baseline values: *$P < 0.05$; **$P < 0.01$.

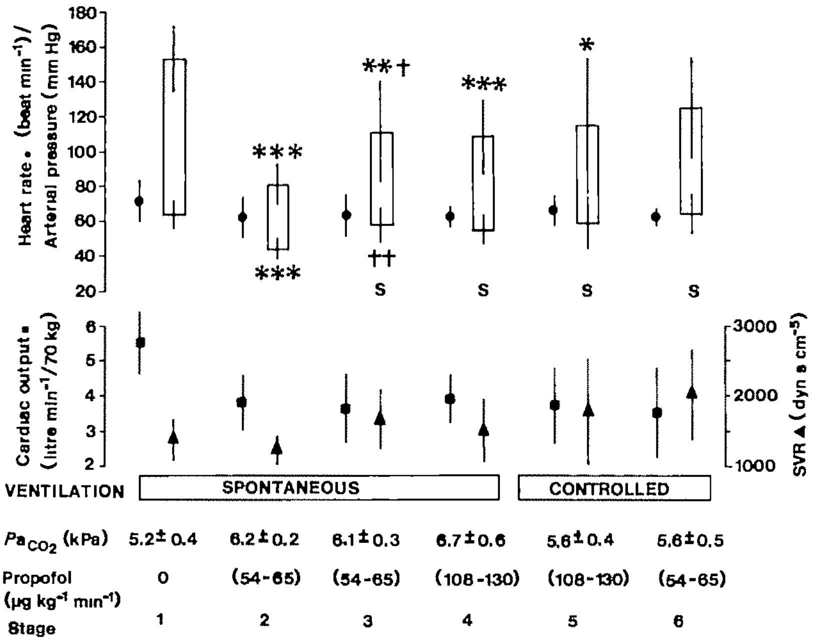


FIG. 2. Haemodynamic responses (mean ± SD) to infusion of propofol during nitrous oxide anaesthesia. Stage numbers are indicated in the text. S = Surgery. Compared with baseline values: $^*P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$. Compared with previous values: $^{\dagger}P < 0.05$; $^{\dagger\dagger}P < 0.01$.

volume (−11%) and SVR (−6%). An increase in the Pa_{CO_2} ($P < 0.05$) reflected an impairment of ventilation.

Systolic (+53%) and diastolic (+47%) arterial pressures, and heart rate (+15%), increased in response to laryngoscopy and tracheal intubation from pre-laryngoscopy values (which had decreased further during the 9 min from induction (fig. 1)). The mean values of these variables following laryngoscopy did not significantly exceed those in the awake patients.

The haemodynamic and Pa_{CO_2} values measured during steady-state anaesthesia at each stage of the study are shown in figure 2. Before surgery (stage 2) the heart rate, systolic and diastolic arterial pressures had further decreased to −14% (ns), −47% ($P < 0.001$) and −31% ($P < 0.001$), respectively, of their baseline values. These changes were associated with a significant ($P < 0.005$) decrease in cardiac output (−31%), and lesser—but insignificant—decreases in stroke volume (−18%) and SVR (−11%). A greater degree of ventilatory depression produced an increase in Pa_{CO_2} ($P < 0.001$).

Surgical stimulation (stage 3, IR_1) was associated with increases in heart rate, systolic ($P < 0.02$) and diastolic arterial pressures ($P < 0.005$) when compared with stage 2. The increase ($P < 0.02$) in SVR accounted for the increase in arterial pressures, the further decrease in cardiac output being non-significant. Surgery did not provide enough stimulation to increase ventilation sufficiently to decrease Pa_{CO_2}.

At the higher infusion rate (stage 4, IR_2) associated with spontaneous ventilation no patients moved in response to surgery and no gross ventilatory depression developed. A complete set of haemodynamic measurements was feasible in all eight patients. The resultant increase in Pa_{CO_2} (+0.6 kPa) was not associated with any significant haemodynamic changes, although the SVR decreased by −11%.

The introduction of controlled ventilation to maintain the end-tidal carbon dioxide at about 5.3 kPa was well tolerated. At the higher infusion rate (stage 5, IR_2) there were no significant haemodynamic changes compared with stage 4 (IR_2). The subsequent decrease in the infusion rate (stage 6, IR_1) caused no marked haemodynamic changes: the increase in SVR (+14%) failed to reach significance. Measurements in this final stage were not completed in one patient because the arterial catheter became occluded.

We compared haemodynamic measurements at the reduced infusion rate during IPPV (stage 6, IR_1) with those obtained with the lower infusion

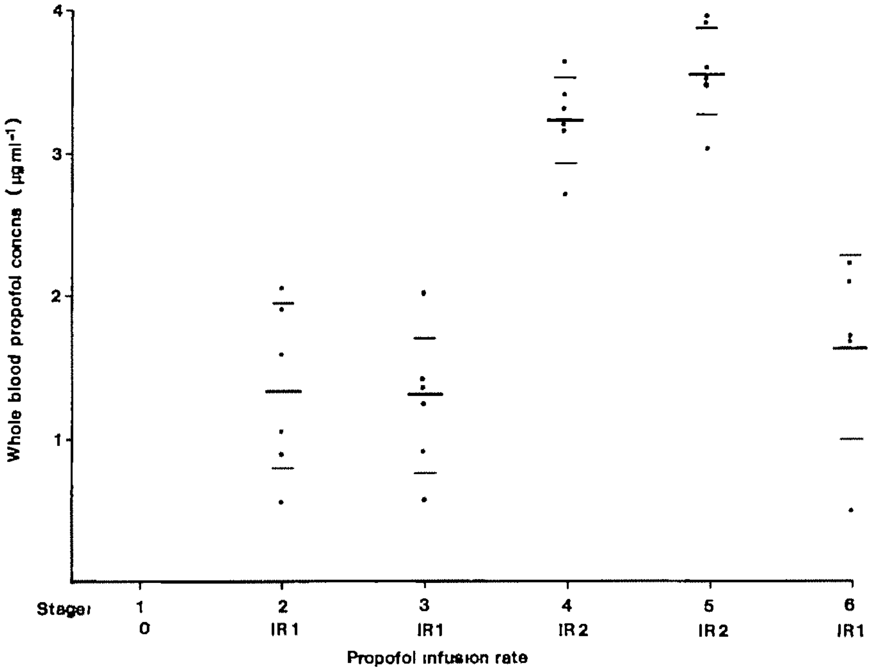


FIG. 3. Whole blood propofol concentrations in six patients measured at stages 1–6, and relevant infusion rate of propofol (IR_1, IR_2). Mean values (heavy line) and standard deviations (light lines) are identified.

rate during spontaneous ventilation (stage 3, IR_1). During controlled ventilation the systolic and diastolic arterial pressures were greater (+14%) and (+10%), respectively, being associated with a decrease in cardiac output (−3%) and an increase in SVR (+19%).

The median duration of the propofol infusion was 258 min (range 164–640 min). The median time to a response to command was 6.9 (range 1–7) min and the time to correct birthdate recall was 12 (range 6–24) min. No venous sequelae developed from the propofol infusion. No patient was able to recall any event during the period of anaesthesia and surgery.

Figure 3 shows the whole blood propofol concentrations at each stage of the study. The mean values during stages 2, 3 and 6 (IR_1) were not significantly different from each other. The mean values during stages 4 and 5 (IR_2) were not significantly different from each other, but were approximately double ($P < 0.001$) the mean values during stages 2, 3 and 6.

DISCUSSION

As a result of studies which identified Cremophor EL as a potential allergen (Glen et al., 1979; Radford, Lockyer and Simpson, 1982), Althesin is no longer available. For the same reason, the original formulation of 2,6-diisopropyl phenol in Cremophor EL was withdrawn. Concern has also been expressed at the effect of etomidate, administered as a continuous infusion, on the suppression of cortisol production (Kenjon, McNeil and Fraser, 1985). Thus, until recently, only methohexitone remained as a suitable drug for infusions of moderate duration (Prys-Roberts, Sear et al., 1983). The introduction of a new formulation of 2,6-diisopropyl phenol, emulsified in soy bean oil, required the reassessment of its haemodynamic effects when administered by continuous infusion.

The minimum infusion rate (MIR), defined as the infusion rate of an i.v. anaesthetic that suppresses movement to the initial surgical stimulation in 50% of patients (ED_{50}), was proposed as an index of anaesthetic potency comparable to MAC for an inhalation agent (Sear and Prys-Roberts, 1979b). We have used this index as a means of comparing the effects of continuous infusions of i.v. anaesthetics on the cardiovascular system (Prys-Roberts, 1982). Our longitudinal series of studies (Sear and Prys-Roberts, 1979a; Sear et al., 1981; Prys-Roberts, Davies et al., 1983; Prys-Roberts, Sear et al., 1983; Coates et al., 1987) of various i.v. anaesthetics have been carried out in such a way that each study has followed a set programme similar to that used in the present study. In this way we can compare the haemodynamic effects of equipotent concentrations of i.v. anaesthetics during spontaneous ventilation, with and without the influence of surgical stimulation, and also the effects of controlled ventilation at a normal Pa_{CO_2} during surgery.

We have recently reported the haemodynamic effects of a continuous infusion of propofol in patients undergoing body-surface surgery (Coates et al., 1987). In the present paper we describe studies of an older group of patients requiring peripheral arterial surgery. Although they had atheromatous arterial disease of their lower limbs, they gave no history, and showed no signs, of coronary artery disease, hypertension, insulin-dependent diabetes, cerebrovascular disease or impaired liver function. In this study we were able to investigate the effects of two infusion rates producing two ranges of blood concentrations of propofol, with either spontaneous or controlled ventilation, allowing comparisons with previous studies.

The infusion strategy used in these studies allowed stable plasma concentrations of propofol to be achieved within 40 min of the induction of anaesthesia; thus the values during stages 2, 3 and 6 were similar and did not indicate a progressive cumulation of the drug. The values during stages 4 and 5 were approximately double those during the other stages, and were similar to those found at similar infusion rates in younger patients (Coates et al., 1987).

The haemodynamic responses to induction in this study were similar to those described by others for the new formulation of 2,6-diisopropyl phenol (Patrick et al., 1985; Coates et al., 1986; Grounds, Moore and Morgan, 1986; Williams et al., 1986), for the Cremophor EL formulation of 2,6-diisopropyl phenol and for other i.v. induction agents used under comparable conditions (Sear and Prys-Roberts, 1979a; Sear et al., 1981; Prys-Roberts, 1982). A wide range of responses was observed in the present study, the extreme being represented by one patient in whom SAP decreased to 38% of the baseline value with reductions in CO and SVR of 33% and 42%, respectively. These changes were not associated with a bradycardia and were treated by transient head-down tilt and an infusion of crystalloid fluid.

The haemodynamic response to laryngoscopy and tracheal intubation, characterized by tachycardia and systolic hypertension, was partly suppressed (Coates et al., 1986). The increase in mean values of heart rate and systolic and diastolic arterial pressures, from the decreased values following induction of anaesthesia, did not significantly exceed the awake baseline values. These responses were less marked than those seen following induction using an infusion of methohexitone (Prys-Roberts, Sear et al., 1983).

Unlike the marked dose-dependent effect of volatile anaesthetics on the heart and peripheral vasculature (Stevens et al., 1971; Prys-Roberts et al., 1974; Calverley et al., 1978), we found no evidence of enhanced haemodynamic effects at the higher infusion rate, in keeping with the results with other i.v. anaesthetics (Prys-Roberts, 1982).

The haemodynamic changes with the two infusion rates with spontaneous or controlled ventilation were comparable to previous studies. The increase in systemic vascular resistance and decrease in cardiac output when comparing controlled with spontaneous ventilation at either infusion rate (stages 6 *v.* 3:5 *v.* 4) could reflect the effect of changes in Pa_{CO_2} upon the cardiovascular system (Prys-Roberts et al., 1968). The decreases in arterial pressures induced by both infusion rates were the result of decreased systemic vascular resistance rather than cardiac output. We have noted in this, as in previous studies, low arterial pressures during maintenance i.v. anaesthesia in the absence of surgical stimulation. Provided the duration of such a period is limited, we have no evidence that this is a major disadvantage for the patient.

Recovery following the simultaneous stopping of the nitrous oxide and propofol, as measured by the times to response to command and to correctly recalling birthdate, was not delayed when compared with infusions of Althesin (Sear and Prys-Roberts, 1979a) or to either the old (Prys-Roberts, Davies et al., 1983) or new (Coates et al., 1987) formulations of 2,6-diisopropyl phenol. Indeed, the rapid and complete recovery following prolonged anaesthesia (average 4 h) was remarkable in that the patients were fully orientated in time and place.

This study, showing minimal haemodynamic changes during surgery with spontaneous or controlled ventilation, the lack of motor response to surgery and the short recovery times, suggests that propofol is an acceptable agent with which to maintain anaesthesia for a prolonged period in elderly patients.

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EFFECTS OF ETHANOL ON PSYCHOMOTOR PERFORMANCE

D. FAGAN, B. TIPLADY AND D. B. SCOTT

SUMMARY

Three separate doses of alcohol (0.2, 0.4 and 0.8 g kg^{-1}) were given to eight volunteers and compared with the effects of a placebo. The order of administration was randomized and the study performed double-blind. A battery of psychometric tests sensitive to central nervous system depression was repeatedly performed for 3.5 h. Alcohol, even in the highest dose, had little effect on psychomotor performance.

Increasingly, psychomotor tests are being used to detect impairment of cerebral function following the administration of drugs used before, during and after anaesthesia. The tests provide a quantitative measure of motor and cognitive function and allow comparison between different drugs or between different doses of the same drug.

The sensitivity of individual tests, and the implications of deviations from normal following the administration of drugs are not clear. Nevertheless, recommendations are made that, on the basis of evidence of residual impairment on one or more tests, the patient should not be allowed to drive home or even discharged from hospital.

Alcohol is a central nervous system depressant and its effects should be easily quantifiable by modern psychometric testing. As most people have experience of its effects, and legal limits for driving have been set, alcohol provides a convenient yardstick against which to compare the depressant effects of other drugs.

Patients frequently ignore warnings to the contrary and take alcohol together with prescribed drugs. Knowledge of its interaction with such drugs is, therefore, of great importance in assessing safety. It is also important to know the effects of alcohol on its own before deciding whether an interaction is additive or synergistic.

The following study was carried out to assess the effects of three different doses of alcohol, using a series of psychomotor tests—all of which have been shown to be sensitive to commonly used sedative drugs.

SUBJECTS AND METHODS

Eight healthy non-alcoholic males consented to take part in this study, which was approved by the local ethics advisory committee. The subjects were aged between 19 and 39 yr (mean = 25 ± 7 SD) and weighed between 59 and 86 kg (mean = 73 ± 8 SD). On each of four sessions they were randomly allocated to receive ethanol 0, 0.2, 0.4 or 0.8 g/kg body weight. The ethanol was given as a solution of 37.5% Smirnoff vodka made up to 500 ml with water and strong orange juice. Blinding was achieved using 5-mg benzocaine lozenges (Tyrosets) and menthol sweets (cherry menthol Tunes) to mask taste and smell. The drink was consumed over a 10-min period on an empty stomach. Subjects were not allowed to smoke or to drink other alcoholic or caffeine-containing beverages from 6 p.m. the previous night until the end of each test session.

Blood samples (5 ml) for the estimation of plasma ethanol concentration were drawn at 0, 10, 20, 30, 45, 60, 75, 90, 105, 120 and 180 min after ingestion.

Subjective measures of performance were recorded using linear visual analogue scales. The subjects were asked to rate how they felt by marking across 10-cm lines, the ends of which read alert/drowsy, steady/dizzy and bored/interested.

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Objective assessments of psychomotor performance were made using tests of choice reaction time (CRT), choice reaction latency (CRL), critical flicker frequency (CFF), body sway (BS), continuous attention (CAT), decision making time (DMT) and auditory vigilance (AV). CRT and CRL were measured using a Leeds Psychomotor Tester (Hindmarch and Parrot, 1978) which measured both the delay in response and the total response time to a visual stimulus. CFF was also measured with the Leeds Tester: the subjects' task was to discriminate the frequency at which flickering lights were just perceived to be "steady" and *vice versa*. BS was measured in the anterior–posterior plane using a Wright–Codoc ataxiameter (Wright, 1971) which detected and measured sway in the erect subjects. CAT consisted of brief presentations of random block patterns on a microcomputer screen; the subject had to respond whenever two consecutive patterns were the same (Tiplady, 1985). The number of correct and incorrect responses were computed. DMT was also a computerized task. A series of pictures of animals and objects were presented to the subjects, who were timed in their response to the question "Is it an animal?" (Tiplady, 1985). Last, in the AV test a series of short tones was played through headphones at 2-s intervals for 1 h. The subject's task was to identify 90 shorter tones randomly presented within the hour (Wilkinson, 1968).

Testing was carried out at 0, 30, 60, 120, 150 and 180 min after the ingestion of the alcohol, with the exception of AV which was assessed between 60 and 120 min.

Statistical analysis was performed using the Friedman rank sum method (*F*) followed by Page's L Trend test (*L*) (Hollander and Wolfe, 1973).

RESULTS

The mean plasma ethanol concentrations are shown in figure. 1. Every subject reached or surpassed the British legal limit for driving with the high dose, but not with the lower doses. Peak plasma concentrations were measured 30–65 min after the strongest drink.

The data obtained from the psychometric tests and the visual analogue scales are shown in figures 2–4. Baseline values corresponding to 0 h for tests in figures 3 and 4 are shown in table I. There were no significant differences in the baseline scores between sessions.

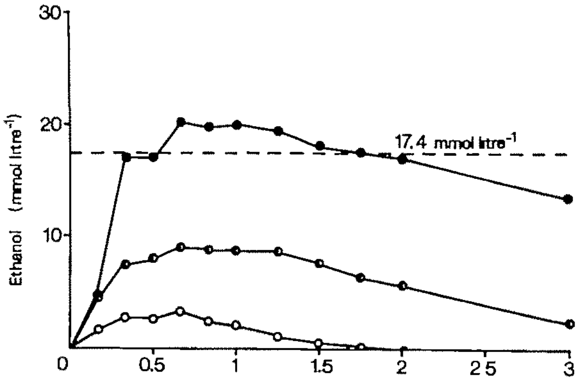

FIG. 1. Plasma concentrations of ethanol in the three active treatment sessions. Figures are means. ○——○ = 0.2 g kg^{-1}; ◐——◐ = 0.4 g kg^{-1}; ●——● = 0.8 g kg^{-1}; ---- = British legal limit for driving.

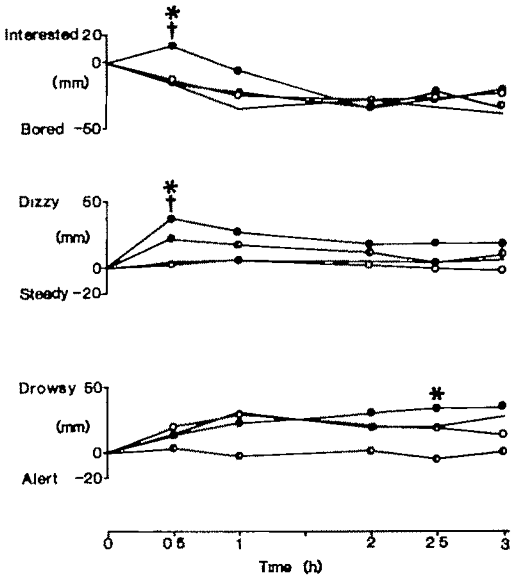

FIG. 2. Subjective effects of ethanol. Scores were calculated as mean changes from the baseline value (mm). —— = Placebo; ○——○ = 0.2 g kg^{-1}; ◐——◐ = 0.4 g kg^{-1}; ●——● = 0.8 g kg^{-1}. *$P < 0.05$ *F* (at least); †$P < 0.05$ *P* (at least).

The peak subjective effects occurred at 0.5 h, while the peak psychomotor effects occurred at 2.5 h.

All of the analogue scales showed statistically significant effects, subjects showing greater interest ($P < 0.05$ *F*, *L*) and dizziness ($P < 0.05$ *F*, $P < 0.01$ *L*) 30 min after drinking the greatest dose of ethanol. Increased drowsiness, however,

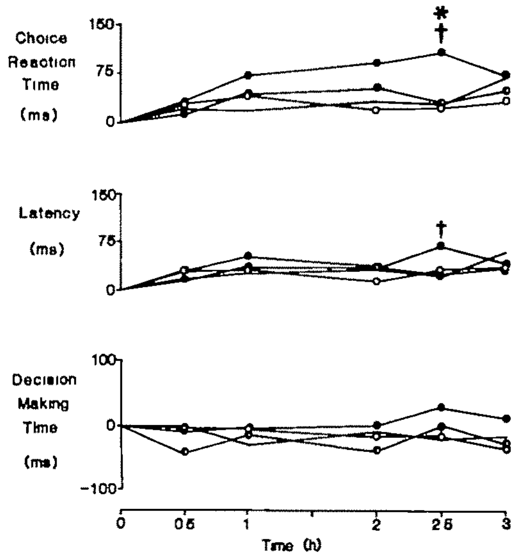

FIG. 3. Effects of ethanol on psychomotor performance. Choice reaction time, latency and decision making times were the means of 30 measurements. Scores were calculated as mean changes from the baseline value. —— = Placebo; ○——○ = 0.2 g kg^{-1}; ◐——◐ = 0.4 g kg^{-1}; ●——● = 0.8 g kg^{-1}. $*P < 0.05$ F (at least); $\dagger P < 0.05$ P (at least).

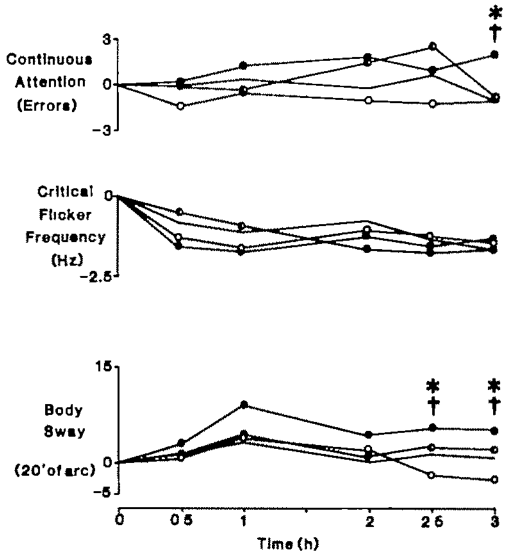

FIG. 4. Effects of ethanol on psychomotor performance. The false positive and false negative scores were summed to give an overall score for continuous attention. The maximum possible error score for CAT was 120. For critical flicker frequency the mean of 6 ascending and 6 descending values was taken. Two 1-min determinations of sway were made. All scores were calculated as mean changes from the baseline value. —— = Placebo; ○——○ = ethanol 0.2 g kg^{-1}; ◐——◐ = 0.4 g kg^{-1}; ●——● = 0.8 g kg^{-1}. $*P < 0.05$ F (at least); $\dagger P < 0.05$ P (at least).

was not apparent until the 2.5-h test period ($P < 0.05$ F).

There were few statistically significant objective effects of ethanol, and those which were in evidence occurred late. CRT and CRL were not significantly prolonged until 2.5 h after the 0.8-g kg^{-1} dose, while sway was only significantly increased at 2.5 and 3 h (all $P < 0.05$ F, L) despite the trend appearing earlier. The total number of errors (omission plus commission) increased at 3 h for the CAT test ($P < 0.005$ F, $P < 0.01$ L), although there was a tendency for scoring to improve with the 0.2-g kg^{-1} dose (not significant). CFF tended to be decreased by the ethanol, and DMT prolonged (not significant). The scores for AV and the errors of commission are shown in table II. The number of correct responses for AV was inclined to decrease at the higher doses, while the AV error scores tended to increase with the highest dose only (not significant). Ethanol had no significant effect on the DMT errors.

TABLE I. *Baseline (pre-drug) values (mean (SD)) for psychomotor tests. CRT = choice reaction time; CRL = choice reaction latency; DMT = decision making time; CAT = continuous attention task; CFF = critical flicker frequency; BS = body sway*

			Ethanol					
Test	Placebo		0.2 g kg^{-1}		0.4 g kg^{-1}		0.8 g kg^{-1}	
CRT (ms)	485	(71)	481	(44)	489	(64)	478	(64)
CRL (ms)	313	(45)	312	(38)	309	(59)	311	(44)
DMT (ms)	502	(86)	495	(77)	542	(122)	505	(106)
CAT (correct)	18	(1)	17	(3)	17	(2)	18	(2)
CFF (Hz)	33.2	(3.5)	32.9	(4.4)	33.1	(4.4)	32.8	(4.2)
BS (20′ arc)	10	(4)	11	(6)	12	(4)	10	(5)

TABLE II. *Effects of ethanol on correct and error scoring for auditory vigilance, and on error scoring for decision making. The maximum possible number of correct scores for auditory vigilance was 90, and the maximum number of false positive errors 1710. As so few errors for decision making were made, these were expressed as errors/day after ingestion. The maximum possible number of errors/day for decision making was 150*

Test	Placebo	Ethanol			Friedman ANOVA	Page's L-trend
		0.2 g kg^{-1}	0.4 g kg^{-1}	0.8 g kg^{-1}		
AV	46.3 (11.9)	47.0 (5.6)	33.2 (11.6)	40.8 (10.8)	ns	ns
AV errors	12.7 (11.9)	14.0 (12.9)	10.3 (8.7)	22.3 (10.9)	ns	ns
DMT errors	2.8 (4.5)	4.3 (3.5)	2.0 (2.8)	3.8 (5.6)	ns	ns

DISCUSSION

The most notable result of this study was how little effect quite high doses of alcohol had on the psychomotor tests used. This cannot be attributed to a general lack of sensitivity of the tests, since previous studies have shown that they are easily capable of detecting the effects of moderate doses of other central depressant drugs (Hindmarch, 1979; Scott, Fagan and Tiplady, 1982; Fagan, Scott and Tiplady, 1984; Swift, 1984). Figure 5 shows a composite graph of results of body sway, measured in our laboratory, after the highest ethanol dose compared with results associated with normal clinical doses of amitriptyline, temazepam, chlormethiazole and zimelidine.

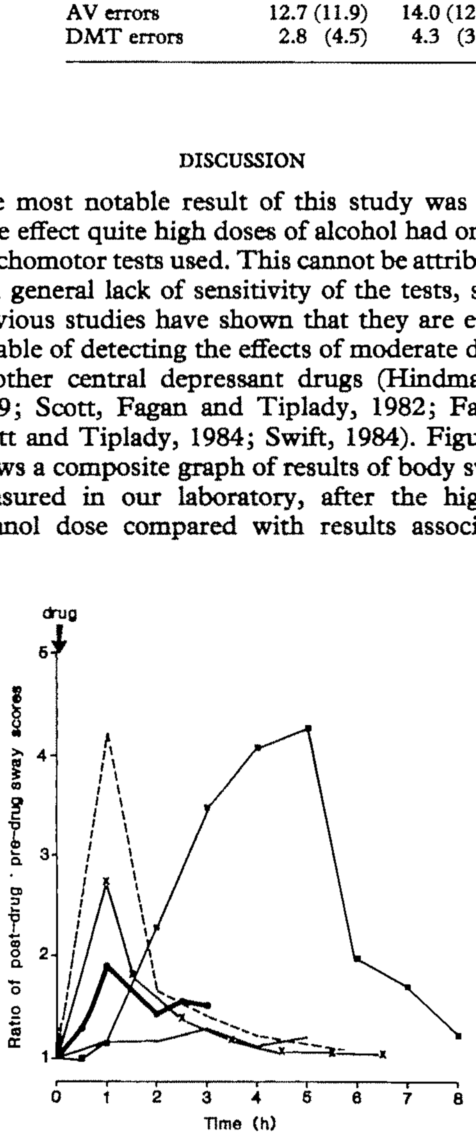

FIG. 5. Composite graph of the acute effect of central depressants on sway in healthy volunteers. The scores are presented as post-drug:pre-drug ratios for each drug. ●——● = Ethanol 0.8 g kg^{-1}; ■——■ = amitriptyline 75 mg; ×——× = chlormethiazole 452 mg; ---- = temazepam 20 mg; —— = zimelidine 200 mg.

At the highest dose, our volunteers were taking one-quarter to one-third of a bottle of vodka, yet the reaction times and sway scores of most were only affected minimally when the plasma concentrations reached their peak. Indeed, the statistically significant results of the objective tests only appeared in the "hangover" period, some hours later, by which time the plasma concentrations were lower and the subjects felt drowsy.

Several other authors have reported a lack of strong deleterious effect on many psychomotor skills using similar doses of alcohol (Palva et al., 1979; McManus et al., 1983). Very high doses of alcohol have to be taken before marked impairment of psychomotor function is seen consistently, especially in younger male subjects. Palva and co-workers (1979) found that their subjects' performance on a reaction time task actually improved with doses of ethanol up to 0.8 g kg^{-1}, and was still not significantly impaired even after 1.2 g kg^{-1} taken acutely. Changes in responses on an attention task were, however, detected at lower doses. Interestingly, the subjective tests seemed to be more sensitive at picking up the central nervous system effects during the acute phase after alcohol.

We do not infer from our results that it is safe to drink and drive or that the legal limit is too low. The well-known propensity for individuals to behave inappropriately while driving with quite low plasma ethanol concentrations would obviate that opinion. Our concern is that other depressant drugs in normal therapeutic doses cause much greater impairment than large amounts of alcohol, but warnings are much less strident and are frequently ignored. Moreover, since small amounts of alcohol can potentiate the effects of many of these drugs (Ferrara, Pikkarainen and Mattila, 1982), the resulting hazard to patients is likely to be considerable.

Using alcohol as a yardstick, measurable abnormalities in the tests used in this study would indicate significant depression, with inability to perform complicated tasks such as driving or operating machinery.

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COMPARISON OF THE EFFECTS OF ATROPINE AND GLYCOPYRROLATE ON COGNITIVE FUNCTION FOLLOWING GENERAL ANAESTHESIA

K. H. SIMPSON, R. J. SMITH AND L. F. DAVIES

SUMMARY

Tests of orientation, concentration and short-term visual memory were used to assess 72 patients 1 day before, and 2 days after, elective major surgery. Patients were premedicated with papaveretum and either atropine or glycopyrrolate, before receiving a standard general anaesthetic. Those who had received atropine showed significant postoperative short-term memory deficit ($P < 0.01$), but no change in orientation or concentration. Those who had been given glycopyrrolate showed no significant cognitive changes after surgery. As glycopyrrolate does not cross the blood–brain barrier freely, these findings support the involvement of central cholinergic mechanisms in the deterioration of cognitive function in the postoperative period.

General anaesthesia has been implicated as a cause of deterioration in postoperative cognitive function (Smith et al., 1985). Complex memory tasks remain impaired for a few days after anaesthesia, although immediate memory, tested by digit span, recovers quickly (Flatt, Birrell and Hobbes, 1984). It has been shown that cognition deteriorates independently of the level of peroperative ventilation, as long as severe hypocarbia is avoided (Blenkarn et al., 1972; Murin and Nagajan, 1974).

Memory involves central cholinergic transmission (Deutsch, 1971). Drugs acting on cholinergic systems have been evaluated in terms of their effects on the attention and memory aspects of information processing (Warburton and Wesnes, 1984). Anticholinergic agents are widely used in anaesthesia as premedicants and for the reversal of neuromuscular blockade. It is postulated that drugs affecting central cholinergic synapses may be important in the production of postoperative cognitive deficits. The involvement of central cholinergic pathways may be assessed by a comparison of atropine and glycopyrrolate, as the latter does not cross the blood–brain barrier freely (Proakis and Harris, 1978).

PATIENTS AND METHODS

Ethical approval was granted for the study which involved 72 fit patients of either sex, aged 27–87 yr, scheduled for elective major general, gynaecological or orthopaedic surgery. Patients taking anticholinergic or sedative medication were excluded, as were those who were to have "psychologically traumatic" operations such as mastectomy, or surgery for known malignancy. Patients were excluded if assessment was anticipated to be difficult or unreliable, for example because of old age or deafness.

On the day before surgery patients were given a small battery of psychometric tests by a clinical psychologist. These tests were repeated 2 days after surgery; patients who were in obvious pain or who had postoperative complications, which could interfere with testing, were then excluded. The following tests were used:

Orientation. In order quickly and easily to assess orientation in time and place, patients were asked 17 questions and one mark was scored for each

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correct answer. The questions were developed from the Wechsler Memory Scale, which has been used to study patients with organic brain damage (Wechsler, 1945). This test also detects reversible toxic confusional states and has proved sensitive to postoperative disorientation in elderly patients (Smith et al., 1985).

Concentration. Patients were asked to recite the months of the year backwards, starting with December. Their speed was recorded, adding 10 s for every error or omission.

Visual memory. The Objective Learning Test (OLT) was used to assess visual short-term memory. This involves the recall of pictures of every day objects—presented on four cards having 10, 15, 20 and 25 items per card. After 3 s viewing time per object, subjects were asked to recall as many items as possible in any order with no time limit. The maximum score possible is 70. The OLT forms half of the Kendrick Battery for the Detection of Dementia in the Elderly (Kendrick, 1972; Gibson and Kendrick, 1979).

Patients received premedication, 1 h before anaesthesia, of papaveretum i.m. (> 70 kg, 20 mg; 50–70 kg, 15 mg; < 50 kg, 10 mg), and either atropine 0.6 mg i.m. or glycopyrrolate 0.2 mg i.m.. The anticholinergic drugs were given in a double-blind randomized manner, in doses recommended for adult premedication (McCubbin et al., 1979; Mirakhur, Dundee and Connolly, 1979). Anaesthesia was induced, using thiopentone 3–5 mg kg^{-1}. A competitive neuromuscular blocking drug was used to facilitate intubation of the trachea, and ventilation with 66% nitrous oxide and oxygen (minute volume 120 ml kg^{-1}; tidal volume 10 ml kg^{-1}). Anaesthesia was maintained using fentanyl (> 70 kg, 0.15 mg; 50–70 kg, 0.1 mg; < 50 kg, 0.05 mg), supplemented with 0.5% halothane, if necessary. After surgery neuromuscular blockade was antagonized with neostigmine 2.5 mg. The same anticholinergic drug which had been given for premedication, either atropine 1.2 mg or glycopyrrolate 0.6 mg, was administered also. The time from induction of anaesthesia to reversal of blockade was noted. Postoperative pain was treated with papaveretum i.m., given on demand in the same dose as for premedication and, if necessary, postoperative emesis was treated with prochlorperazine.

Data were analysed using Student's *t* test for independent samples, Chi-squared, Pearsons Product Moment Correlation Coefficient or two-way analysis of variance for repeated measures, followed by the Tukey test as appropriate.

TABLE I. *Demographic data and duration of surgery*

	Atropine ($n = 30$)	Glycopyrrolate ($n = 30$)
Age (yr)		
Range	30–83	27–87
Mean (SEM)	49.3 (2.8)	50.6 (3.0)
Weight (kg)		
Range	60–95	55–85
Mean (SEM)	68.9 (1.7)	69.6 (1.1)
Sex	3M, 27F	4M, 26F
Duration of surgery (min)		
Range	15–280	15–260
Mean (SEM)	65.8 (10.2)	61.5 (8.1)

RESULTS

Twelve patients were excluded from the study after postoperative assessment: 10 were in obvious pain, one had bled during the previous night and one was pyrexial. The remaining two groups of 30 patients were analysed. The sex distribution, ages and weights of the two groups were not significantly different (table I). The doses of papaveretum (as premedication), thiopentone and fentanyl did not differ significantly between the groups. Twenty of the atropine and 22 of the glycopyrrolate group received halothane. The duration of surgery in the groups was not significantly different (table I). There were no significant differences between the groups in the number of doses of papaveretum or prochlorperazine given in the first 2 days after operation.

There were no significant changes in pre- to postoperative concentration or orientation scores in either group. Significant postoperative memory deficit was found in the atropine group ($F = 7.09$, $P < 0.01$), but not in the glycopyrrolate group (table II). The performance of more patients on memory testing was worse following surgery after atropine (77%), compared with after glycopyrrolate (43%) ($P < 0.05$). Short-term memory deficit did not correlate significantly with age ($r = 0.26$) or duration of surgery ($r = 0.10$).

DISCUSSION

Several studies have suggested that learning initiates a neuronal process in which excitability at cholinergic synapses increases. When learning has

TABLE II. *Mean (SEM) scores on cognitive testing.* **Postoperative score significantly less than preoperative ($P < 0.05$)*

	Atropine ($n = 30$)		Glycopyrrolate ($n = 30$)	
	Before surgery	After surgery	Before surgery	After surgery
Orientation (17 maximum)	16.3 (0.1)	16.2 (0.2)	16.1 (0.2)	16.1 (0.2)
Concentration (s)	21.1 (2.9)	19.3 (2.4)	22.2 (3.1)	26.1 (4.4)
Memory (70 maximum)	41.1 (1.6)	37.3 (1.4)*	39.4 (2.2)	38.9 (2.0)

finished there is a decrease in cholinergic synaptic excitability, which coincides with a natural loss of memory recall (Deutsch, 1971). If changes in cholinergic activity occur during learning it should be possible to show drug-induced facilitation or inhibition of memory.

Facilitation of memory. Animal studies have supported the involvement of cholinergic pathways in learning and memory. Learning was enhanced and errors reduced following low-dose physostigmine (Whitehouse, 1966). High doses gave the opposite effect, perhaps as a result of functional blockade of cholinergic synapses. Similarly, the intracerebral injection of a cholinesterase inhibitor, diisopropylfluorophosphate (DFP) (in rats) caused alteration of recall of learned behaviour for several days after training (Deutsch, Hamburg and Dahl, 1966). Comparable effects were produced using physostigmine (Hamburg, 1967). Because of adverse muscarinic effects, these agents are difficult to evaluate in humans.

Impairment of memory. There is evidence for impairment of the information input component of memory following cholinolytic agents such as atropine (Whitehouse, 1964) and hyoscine (Carlton and Vogel, 1965). Several studies in man have confirmed the findings in animal models. It has been suggested that there is impairment of memory storage, and possibly retrieval, following hyoscine, despite normal immediate memory span (Drachman and Leavitt, 1974). Hyoscine reduced performance on some subsets of the Wechsler Memory Scale, but not digit recall, which tests immediate memory (Ostfeld and Aruguette, 1962). Safer and Allen (1971) reported grossly impaired delayed recall of digits after hyoscine. It has also been shown that hyoscine 0.4 mg i.m. decreased ability for immediate and delayed recall of lists of words (Anderson, McGuire and McKeown, 1985). Clinically, atropine is known to produce central effects including disorientation, hallucinations and memory loss (Longo, 1966). Atropine 2 mg i.m. affected both performance on digit span and short-term memory (Wetherell, 1980). When patients who had received atropine 0.6 mg were compared with those who had received placebo, the former showed impaired backward digit span, but normal immediate and delayed recall (Anderson, McGuire and McKeown, 1985). Cognitive effects of atropine may be dose-dependent, and more than 0.6 mg may be necessary for profound effects. Therefore, deficits may be more pronounced in patients who are paralysed and ventilated artificially, as they commonly receive atropine 0.6 mg as premedication and 1.2–1.8 mg with antagonism of neuromuscular blockade. In support of central cholinergic involvement, post-anaesthetic arousal times and recovery after glycopyrrolate have been shown to be superior to atropine (Baraka et al., 1980; Sheref, 1985).

The present study supports the envisaged role of central cholinergic mechanisms in cognitive function. Thus, in terms of postoperative cognition, glycopyrrolate may be a preferable alternative to atropine.

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COMPARISON OF RECOVERY AFTER HALOTHANE OR ALFENTANIL ANAESTHESIA FOR MINOR SURGERY

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SUMMARY

Recovery after anaesthesia was assessed using the Maddox Wing Test (MW), Critical Flicker Fusion Threshold (CFF), Choice Reaction Time (CRT), Line Analogue Rating Scales (LARS), a Tracking Test and a test of Semantic Memory in 44 patients who had undergone minor gynaecological surgery. The patients were allocated randomly to one of two groups and received either methohexitone, nitrous oxide, oxygen and halothane or methohexitone, alfentanil, nitrous oxide and oxygen. Immediate recovery was more rapid in the alfentanil group ($P < 0.01$), but apnoea ($P < 0.05$) and hiccups ($P < 0.05$) were more common. Except for the CFF test, which showed the alfentanil patients to be less sedated than the halothane patients on the morning after anaesthesia ($P < 0.05$), the results of the tests were similar in both groups and showed, initially, substantial impairment of psychomotor functions which gradually returned to baseline values. This comparison with halothane anaesthesia indicates that a technique using methohexitone and alfentanil is suitable for day-case surgery.

Alfentanil, a synthetic opioid analgesic, with a rapid onset, and short duration, of action (Niegmegeers and Janssen, 1981; Sinclair and Cooper, 1983) has great potential for use in day-stay patients in whom rapid recovery of physical and mental function is necessary. However, somewhat conflicting results have been obtained: some workers (Kay and Venkataraman, 1983; Antonios, Inglis and Lees, 1984; Waldron and Cookson, 1984) found that alfentanil produced more rapid recovery than traditional anaesthetic agents, whereas others (Cooper et al., 1983) were unable to discriminate between the recovery of patients treated with alfentanil or fentanyl. Rapid initial recovery from alfentanil has been described (Inglis, 1983; Kay and Venkataraman, 1983), but there has been no clear demonstration of an effect on psychomotor performance. The purpose of the present investigation was to assess recovery after a standard anaesthetic regimen (methohexitone, nitrous oxide and halothane) and to compare it with one using alfentanil. The test procedures were devised to assess the physical and mental aspects of recovery over a 19-h recovery period.

PATIENTS AND METHODS

The study was approved by the Ethical Committee of Leeds General Infirmary. Forty-four patients aged between 20 and 65 yr who were to undergo D & C or cystoscopy, or both, were admitted to the trial. All gave informed consent to participation, were in good health (ASA grades I and II) and had no history of atopy or of taking psychotropic drugs. They were allocated randomly to one of two groups. Familiarization with the test procedures took place 3–4 h before surgery. All patients practised on the assessments until consistent results were obtained and then baseline (pre-anaesthetic) scores were recorded.

All the operations took place between 14.00 and 15.00 h. The patients had received no sedation the night before surgery and no premedication was given. Patients in the alfentanil group received a bolus dose of alfentanil 250 µg i.v. over 30 s, followed by induction of anaesthesia with methohexitone and maintenance with 66% nitrous oxide, 33% oxygen plus alfentanil 250 µg i.v. 1 min before surgery commenced, and at 5-min

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intervals thereafter. Supplementary doses of methohexitone were given when anaesthesia was too light. In the halothane group, anaesthesia was induced with methohexitone and maintained with 66% nitrous oxide, 33% oxygen and 1–1.5% halothane. All patients breathed spontaneously and any period of apnoea lasting more than 20 s was noted. If postoperative analgesia was required, paracetamol 1 g was given. The durations of surgery and anaesthesia were recorded and the times to opening of eyes and to answering simple questions were noted by the recovery room staff. Any complaint of headache, nausea or vomiting was recorded while the patient was in the recovery room. All testing was carried out in a room off the main ward in which the levels of lighting and noise could be standardized.

The first postoperative test took place 0.75 h after the anaesthetic gases were discontinued and subsequent tests were performed at 1.25, 2 and 3 h. The final series of tests was administered between 09.00 and 10.00 h the next morning—about 19 h later. The computerized tasks were not used in the first two test sessions, since the patients did not have the necessary sensori–motor co-ordination.

Test procedures

Maddox Wing. Centrally-acting drugs impair the fusion mechanism of the eyes and accentuate their deviation. To reveal heterophoria, the balance of the extraocular muscles was measured by means of the Maddox Wing Test (Hannington-Kiff, 1970). The horizontal scale of the device was used and measurements were made in prism dioptres.

Critical Flicker Fusion (CFF). The critical flicker fusion test (CFF) was used as a means of measuring the patient's ability to distinguish discrete sensory data, as an index of their overall CNS activity (Hindmarch, 1982). The mean of the flicker fusion threshold for three ascending and three descending trials was the score used at each test.

Choice Reaction Time (CRT). Choice Reaction Time was used as a measure of sensori–motor performance (Hindmarch and Subhan, 1983). The test box automatically recorded recognition reaction time (RRT) (the time taken to lift the index finger from the rest template and respond to a light stimulus) and total reaction time (TRT) (time to reach the appropriate response button). By subtracting RRT from TRT, the time required for the motor response (MRT) was obtained.

Linear Analogue Ratings Scales (LARS). Subjective ratings of anaesthetic effects were obtained from a set of 10-cm linear analogue rating scales (Hindmarch and Gudgeon, 1980). The "less tired – more tired", "less drowsy – more drowsy", and "less alert – more alert" scales (among eight distractor scales), were taken as a measure of perceived sedation.

Tracking Test. In this test of psychomotor function, patients were required to track an arrow on a BBC microcomputer screen by using a joystick. The movement of the arrow was controlled by a fixed program and the response measure (RMS) was the mean deviation from the track program (calculated as a root mean square (RMS)) over the 1-min trial period. In addition a "peripheral awareness" task was included in which the subject responded to a stimulus presented in the periphery of vision, whilst simultaneously attending to the tracking task. The mean reaction time (RT) to 10 of these peripheral stimuli per trial was also used as a response measure (Hindmarch, Subhan and Stoker, 1983). At each test time five of these trials were given, the first being used as practice and the mean of the next four in the analysis.

Semantic Memory Test. A semantic classification task was presented on a BBC microcomputer. A category name (e.g. ANIMAL) was shown on the VDU followed by a test word (e.g. HORSE). The patient then had to decide whether or not the test word belonged to the specified category and press either a "Yes" or a "No" key to indicate his choice. The mean time taken to categorize the test word for 48 stimulus presentations was the response measure recorded. This test was included to study information processing by measuring changes in classification latencies following anaesthesia.

RESULTS

Forty-four patients consented to participate in the trial and 40 of these completed all the postoperative tests. In the alfentanil group, two patients were withdrawn from the study: one because of a perforated uterus and the other because of sickness and headache. Of the halothane patients, one was unco-operative and another was not returned to the ward in time for testing because of shortage of staff.

TABLE I. *Demographic details*

	Alfentanil group				Halothane group				
	n	Mean	Range	SEM	*n*	Mean	Range	SEM	*P*
Age (yr)	22	40.5	23–51	1.8	22	40.2	21–64	2.6	ns
Weight (kg)	22	67.5	47–108	3.3	21	65.6	52–101	2.6	ns
Mean total dose alfentanil (µg)	22	727	500–1000	37				2.7	
Mean total dose methohexitone (mg)	22	199	100–350	13	21	99	70–115	2.0	ns
Duration of anaesthesia (min)	22	9.6	4.6–20.0	2.7	21	12.7	10–18.2	1.2	< 0.05
Time to open eyes (min)	21	4.6	1.8–10.7	0.9	21	7.5	1.5–16.3	2.8	< 0.01
Time to give name (min)	21	4.7	2.0–7.6	0.6	21	8.1	1.8–16.7	2.9	< 0.01
Time to show thumb (min)	22	5.3	2.2–20.7	2.9	21	8.6	2.2–17.0	3.0	< 0.01

Table I illustrates the demographic details of the patients in each group. There were no significant differences (*t* test) in the ages or weights of the subjects, and all were classed as ASA grade I apart from two (grade II) in the halothane group. The duration of anaesthesia and the three indices of recovery showed a skewed distribution, so the *t* test was performed on logarithmically transformed data. The duration of anaesthesia was significantly shorter for the alfentanil patients than for the halothane patients because it took longer to attain a satisfactory depth of anaesthesia with halothane. The average time from induction until the beginning of surgery was 7.8 min for the halothane group and 4.7 min for the alfentanil group. This difference was significant ($P < 0.001$). Similarly, the times required for patients to open their eyes, give their name and show their left thumb were significantly shorter in the alfentanil group ($P < 0.01$).

Of the forty patients who completed the whole study, 34 were anaesthetized by E.M. and six by R.S.E.; each anaesthetized an equal number of patients from each treatment group. The mean durations of anaesthesia for each of these patient groups were 11.7 min (E.M.) and 10.8 min (R.S.E.). The results of each test were analysed both with and without the six patients anaesthetized by R.S.E. and, since no changes in the significance of the results were observed, data from 40 patients were used in the final analysis.

Table II gives details of the side-effects experienced during anaesthesia and the recovery period. More alfentanil patients became apnoeic during the induction and maintenance of anaesthesia ($P < 0.05$) and the average duration of apnoea was longer with alfentanil (75 s) than with halothane (25 s) ($0.01 > P < 0.001$). Hiccups were significantly ($P < 0.05$, Chi-squared test) more common in the alfentanil group than in the halothane group, but no other differences were significant.

The most notable side effects recorded during the recovery period were headache, nausea and vomiting. There were no differences between the groups in the incidences of these complaints or in requests for analgesia. For the psychological tests, baseline scores are given, together with the mean change from baseline scores (± SEM). Results are given to one decimal place or, where appropriate, whole numbers to simplify tabulation. All statistical computations were performed on raw data correct to two decimal places. The baseline scores for the alfentanil and halothane groups were found to be significantly different in the CFF, Tracking, CRT and Memory Tests. For this reason, all of the results except the subjective assessment of sedation were analysed using a repeated measures analysis of variance on the "change from baseline" scores. Significant changes from baseline scores within the groups can be calculated using the least significant difference (LSD) values. In tables III, IV and VI the LSD score at the 5% level for a one-tail test is given for each test procedure. Any difference which is greater than the LSD value is significant.

TABLE II. *Side effects during anaesthesia and recovery*

	Alfentanil		Halothane		
Side effect	No. patients	No. with symptom	No. patients	No. with symptom	P
During anaesthesia					
Apnoea	22	11	21	3	< 0.05
Apnoea during induction	22	9	21	3	ns
Apnoea during maintenance	22	7	21	0	< 0.02
Involuntary movement	22	4	21	2	ns
Pain on injection	22	6	21	5	ns
Myoclonus	22	2	21	3	ns
Cough	22	2	21	7	ns
Flushing	22	2	21	0	ns
Rigidity	22	4	21	1	ns
Hiccup	22	10	21	3	< 0.05
Laryngospasm	22	3	21	3	ns
Excess salivation	22	2	21	3	ns
Induction unsatisfactory	22	1	21	5	ns
Others	22	2	21	3	ns
During recovery					
Headache	22	6	21	12	ns
Nausea	21	6	21	6	ns
Vomiting	21	5	20	2	ns
Patients requiring analgesics	20	2	20	7	ns
Patients requiring hypnotics	20	8	20	8	ns
Others	20	3	20	2	ns

There was a significant anaesthetic × time interaction in the CFF results ($P < 0.01$) which was still significant ($P < 0.05$) when a conservative F test was used to check for positive bias (Kirk, 1968). In both groups the CFF scores were significantly depressed throughout the afternoon, when compared with their baseline reading. However, on the following morning, the halothane group were still scoring below their baseline, while the alfentanil patients had improved on theirs and were significantly less sedated than the halothane patients (table III).

In the reaction time task, the mean of the 20 trials performed at each test were used in the analysis. In all of the measures (RRT, MRT and TRT), subjects from both groups showed a marked increase in their reaction times after surgery, and all had approximated to their baseline performance levels by the following morning. No significant differences were observed between the two experimental groups on any of these measures at any of the test times (table III).

The Maddox Wing scores were all scored as being positive, whether they were to the left or to the right of zero. Both treatment conditions showed an initial marked increase in their scores after anaesthesia and these gradually decreased between the test sessions to approach baseline values by 3 h. No significant differences were observed between the two groups, although within group changes proved significant (table III).

Possible scores in the LARS ranged from 0 (highly alert) to 100 (highly sedated). The sedation scores of the two treatment groups were compared with each other and no significant differences in perceived sedation were observed. Both groups showed an initial increase in sedation scores which gradually decreased during the test period and by the next morning sedation was perceived to be slightly less than normal (i.e. less than 50) in both groups.

The results of the tracking accuracy (RMS) component indicated that alfentanil patients suffered significant impairment at the 2-h test, but

TABLE III. *Mean values (±SEM) for change from baseline scores on psychological tests and mean values (±SEM) on subjective ratings scores.* *$P < 0.05$ *for a between-group comparison of means. LSD = least significant difference, any change score greater than the LSD is significant, within group, at* $P < 0.05$*; CFF = Critical Flicker Fusion Threshold; RRT = Recognition Reaction Time; MRT = Motor Response Time; TRT = Total Reaction Time; MW = Maddox Wing Test; LARS = Line Analogue Rating Scales*

	CFF (Hz)	RRT (ms)	MRT (ms)	TRT (ms)	MW (dioptre)	LARS (mm)
Alfentanil group						
Pre-test	26.6	383	247	630	3.47	49.5
	(0.7)	(14)	(11)	(17)	(0.7)	(3)
0.75 h	−3.3	81	89	170	2.6	68
	(0.4)	(27)	(45)	(70)	(0.6)	(3)
1.25 h	−3.1	30	44	73	1.1	54
	(0.4)	(15)	(13)	(23)	(0.5)	(4)
2.0 h	−2.9	33	20	53	1.0	50
	(0.3)	(13)	(10)	(16)	(0.6)	(5)
3.0 h	−1.9	14	23	37	0.2	48
	(0.3)	(13)	(7)	(13)	(0.4)	(4)
19 h	1.1*	−4	18	14	0.6	46
	(0.3)	(10)	(11)	(11)	(0.6)	(4)
Halothane group						
Pre-test	27.6	385	261	646	3.2	60
	(0.6)	(9)	(11)	(14)	(0.6)	(4)
0.75 h	−2.5	53	61	114	1.7	69
	(0.5)	(9)	(11)	(17)	(0.5)	(3)
1.25 h	−2.4	45	52	97	1.4	58
	(0.5)	(13)	(14)	(21)	(0.6)	(4)
2.0 h	−2.1	26	23	49	1.3	49
	(0.4)	(11)	(11)	(17)	(0.6)	(4)
3.0 h	−1.5	26	21	49	0.7	53
	(0.3)	(9)	(11)	(15)	(0.5)	(4)
19 h	−0.2	17	11	28	0.5	41
	(0.3)	(13)	(8)	(17)	(0.6)	(3)
LSD 5 % one-tail	0.8	30.6	43.0	67.4	0.9	

TABLE IV. *Change from baseline scores on the tracking task: mean values (±SEM). LSD = Least significant difference; any change score greater than the LSD is significant, within group, at* $P < 0.05$*. RMS = Root mean square units: assessment of tracking accuracy. Higher figures represent more impairment. RT = Reaction time (ms) to peripheral stimulus*

	Alfentanil group		Halothane group	
	RMS (units)	RT (ms)	RMS (units)	RT (ms)
2 h	165 (49)	21 (6)	94 (47)	20 (6)
3 h	4 (47)	35 (6)	−44 (47)	1 (6)
19 h	−149 (47)	−1 (6)	−179 (51)	−22 (7)
LSD	127	17	127	17

by the next morning both groups had significantly improved on their baseline performance (table IV). No significant differences were observed between the groups.

No between-group differences were found in the distraction task (RT). However, a significant impairment at the 2-h test was found following within-group comparisons for both anaesthetics. Those given alfentanil recorded significantly poorer scores at 3 h than pre-test. The performance of patients given halothane was better at 19 h compared with their baseline scores.

TABLE V. *Mean changes (s) from baseline scores on the Semantic Classification Test*

Group	Before test	2 h	3 h	19 h
Alfentanil	105.0	4.5	2.7	−0.5
Halothane	94.7	5.9	1.3	−1.2

During the semantic classification test, two lists were given at each test session and these were analysed together to form one set of scores. Results of this test showed the anaesthetic × time interaction to be non-significant. Overall reaction times were seen to be slower in the first two postoperative tests, but by the next morning both groups had improved very slightly on their baseline scores (table V). Although the negative scores were significantly slower than the positive, no consistent or significant differences were seen between the two treatment groups. Consequently, only data for the overall response times are displayed. Seven patients in the alfentanil group and eight patients in the halothane group received benzodiazepines for night sedation after surgery. It can be seen from table VI, which shows the results of the psychomotor tests with these patients excluded, that postoperative night sedation did not affect the results at 19 h. The CFF score at 19 h in the alfentanil group was significantly greater than the baseline score, whether or not those receiving night sedation were excluded.

DISCUSSION

The aim of this study was to test the recovery of psychomotor function following two very different techniques of anaesthesia, each of which provides good operating conditions for minor gynaecological surgery. As a predominantly i.v. technique was being compared with an inhalation one, it was not possible to compare depths of anaesthesia by giving equal multiples of MAC, so an exact comparison of depth of anaesthesia between the two groups was not feasible. The purpose of general anaesthesia is to abolish the conscious appreciation of surgery and to provide good operating conditions without compromising vital functions, so depth of anaesthesia was judged on clinical grounds, and the minimum quantity of anaesthetic which satisfied these conditions was administered.

The results of this study are similar to those of Antonios, Inglis and Lees (1984), Cartwright (1985) and Waldron and Cookson (1984) and confirm that immediate recovery was significantly more rapid after alfentanil than after halothane. Cartwright (1985) found that apnoea was a problem when alfentanil was compared with halothane. The present study confirmed that apnoea occurred more frequently and was of longer duration with alfentanil than with halothane but, interestingly, the incidence of apnoea was far less common as the study progressed (eight patients experienced apnoea at least once in the first half of the alfentanil group, but only three in the second half). This suggests that the problem is reduced when the anaesthetist is familiar with the technique, as confirmed by Collins and Plantevin (1985).

In the recovery period, headaches were most common and lasted longer in the halothane patients, and sickness was more of a problem in the alfentanil group, but these differences were not significant, and all but five patients were able to complete their assessments. When compared

TABLE VI. *Mean change from baseline scores at 19 h for patients without night sedation.* **P* < 0.05 *for change from pre-test values. CFF = Critical Flicker Fusion Threshold; RRT = Recognition Reaction Time; MRT = Motor Response Time; TRT = Total Reaction Time; MW = Maddox Wing Test; RMS = Root mean square units: assessment of tracking accuracy. Higher figures represent more impairment; RT = Reaction time to peripheral stimulus*

Group	CFF (Hz)	RRT (ms)	MRT (ms)	TRT (ms)	MW (dioptre)	RMS (units)	RT (ms)
Alfentanil ($n = 13$)	1.3*	−5.0	24.2	19.2	0.3	−72.0	9.9
Halothane ($n = 12$)	0.2	1.5	6.4	4.9	0.3	−69.0	−15.9

with inhalation agents, opioid analgesics may produce an increase in the frequency of nausea and vomiting, although the nausea and vomiting reported by Collins and Plantevin (1985) was attributed equally to the effects of alfentanil, the gynaecological surgery and the use of oxytocin.

Results of the postoperative tests were similar in both groups, with an initial large impairment of psychomotor function gradually decreasing during the afternoon and, in the majority of tests, returning to baseline by the next morning. The only assessment to demonstrate a difference between the two anaesthetic techniques was the CFF test, in which patients who received alfentanil were found to be significantly less sedated than the halothane patients on the morning after anaesthesia. On the only other test which approached statistical significance (the RT component of the tracker), the results indicated that the halothane patients recovered more quickly.

The "sedation" scores observed in the present study showed a progressive decrease (apart from a small increase at the 3-h test in the halothane group) and these results indicate that patients felt slightly less tired than normal the morning after anaesthesia. Initially, the choice reaction time test and the Maddox Wing Test demonstrated large increases in scores which gradually decreased during the recovery period, but no differences were observed between the two anaesthetics. Kay and Venkataraman (1983) used the Maddox Wing Test and did show a greater impairment in patients receiving fentanyl 1 h after surgery when the scores of patients in whom anaesthesia was induced with etomidate and maintained with either fentanyl or alfentanil were compared. This suggests that both alfentanil and halothane cause less impairment on this test than does fentanyl. The semantic classification task was perhaps too complex for the situation and appeared to be influenced only by a gross anaesthetic effect.

One of the reasons for using a battery of tests of psychomotor function was to identify which measures provided the most sensitive indication of postoperative recovery of mental function. The present results indicate that CFF, in this situation, is the most sensitive measure and that the other tests fail. The scores on the choice reaction time test and the Maddox Wing returned to baseline earlier than those of the CFF test. In the tracking and categorization tasks, there appeared to be inadequate time for training, because tests on the morning after anaesthesia indicated that performance in both treatment groups had improved on baseline as a result of practice. The essential requirement of adequate practice when using tasks with a pronounced learning effect should be borne in mind in all future investigations of this type.

Patrick and colleagues (1984) found no significant differences between the immediate recovery times (open eyes, name and date of birth) with alfentanil and fentanyl, but did show that the return of motor co-ordination (post-box technique) was more rapid in the alfentanil group. However, when compared with other (Sanders, Sinclair and Sear, 1984; Short, Rutherfoord and Sebel, 1985) or similar (Kay and Cohen, 1984; Kennedy and Ogg, 1985) anaesthetic techniques, alfentanil has been shown to give a faster initial recovery, but then to be similar to other anaesthetics in later tests—findings which are similar to those of this study.

The results of this study show that psychomotor function had not returned to normal for some hours after either anaesthetic technique, confirming the need to warn patients not to perform tasks requiring sensori-motor co-ordination or concentration (e.g. driving a car) for at least 24 h after day-case anaesthesia. Although the administration of night sedation to some of the patients would have been expected to contribute to the impairment of psychomotor function the next morning, no differences were detectable between those who received benzodiazepines and those who did not. Very few studies of alfentanil have involved testing for more than a few hours after surgery. The fact that the CFF scores from the two groups were significantly different on the morning after anaesthesia suggests that it may be useful to lengthen the test period in future studies.

Both of the anaesthetic techniques used in this study proved satisfactory, and the immediate recovery with alfentanil was significantly shorter. The more rapid attainment of surgical anaesthesia and avoidance of volatile anaesthetics which relax the pregnant uterus (Moir, 1970; Naftalin et al., 1977) make the methohexitone–alfentanil technique useful for certain minor gynaecological procedures. The postoperative assessments showed that there was little difference between the profiles of recovery after halothane or alfentanil, although those given alfentanil were significantly more alert (CFF scores) at 19 h than those patients treated with halothane. Comparisons of recovery after day-case anaesthesia with different volatile anaesthetic agents (Carter, Dye and Cooper, 1985) have shown very little difference between halothane, enflurane and isoflurane. Therefore, this comparison with halothane anaesthesia indicates that an anaesthetic technique using methohexitone and alfentanil is suitable for day-case surgery. The CFF test was found to be the most sensitive test of cognitive function following anaesthesia.

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USE OF SIMPLE TESTS TO DETERMINE THE RESIDUAL EFFECTS OF THE ANALGESIC COMPONENT OF BALANCED ANAESTHESIA

T. MANNER, J. KANTO AND M. SALONEN

SUMMARY

In order to evaluate simple means of determining the rate of recovery after general anaesthesia, the usefulness of the critical flicker fusion threshold test, the Maddox wing apparatus and the visual analogue scale were compared. The postanaesthetic recovery score was used as a reference. Two patient groups ($n = 15$ *in each) received, in a randomized double-blind study, a similar balanced anaesthesia for Caesarean section, except that the analgesic component was either fentanyl* 2.5 $\mu g\ kg^{-1}$ *i.v. or buprenorphine* 7.5 $\mu g\ kg^{-1}$ *i.v. Maddox wing apparatus and visual analogue scale were sensitive enough to differentiate between the postanaesthetic residual effects of the two opioids, but critical flicker fusion threshold and, especially, postanaesthetic recovery score were insensitive in this respect. There was no difference between the two patient groups in mean arterial pressure and heart rate. Our results show that the residual effects of different kinds of opioids as an analgesic component of balanced anaesthesia can be differentiated using simple means like Maddox wing apparatus and visual analogue scales.*

Many attempts have been made to define the best methods with which to evaluate recovery from anaesthesia, and the effects of the different drugs used during anaesthesia. In our earlier study (Manner, Kanto and Salonen, 1987) simple tests (Maddox wing apparatus, critical flicker fusion threshold test, visual analogue scale ratings for subjective sensations) differentiated clearly between the effects of fentanyl and those of buprenorphine and, especially, from those of a placebo. We have used the same simple tests to evaluate the difference in the rate of recovery after general anaesthesia when fentanyl or buprenorphine were used as the analgesic component of balanced anaesthesia. The "postanaesthetic recovery score", which has been widely used since 1970, was recorded and used as a reference.

PATIENTS AND METHODS

In a randomized, double-blind study the per- and postoperative effects of fentanyl ($n = 15$) and buprenorphine ($n = 15$) (as the analgesic component of a balanced anaesthetic technique) were recorded in healthy women undergoing elective Caesarean section. The patients were at term, and none had any signs of placental dysfunction. The most common indications for Caesarean section were cephalo–pelvic disproportion and previous Caesarean section. In group 1, after the clamping of the umbilical cord, fentanyl 2.5 $\mu g\ kg^{-1}$ was injected i.v. and in group 2, buprenorphine 7.5 $\mu g\ kg^{-1}$ i.v. Based on clinical studies (Heel et al., 1979; Mather, 1983), and our own experiences with healthy volunteers (Manner, Kanto and Salonen, 1987), the doses chosen were expected to produce a comparable maximal analgesic effect. Otherwise, the anaesthesia (routine technique of J. Kanto) was similar in both groups: no premedication; vecuronium 120 $\mu g\ kg^{-1}$ i.v. followed after 15–30 s by rapidly injected thiopentone 4 $mg\ kg^{-1}$ i.v. + nitrous oxide in oxygen (40:60) + 0.5% halothane (until delivery); maintenance of anaesthesia: nitrous oxide in oxygen + opioid + dihydrobenzperidol 20 $\mu g\ kg^{-1}$

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i.v.; glycopyrrolate 0.4 mg+neostigmine 2.5 mg i.v. After cord clamping, oxytocin 5 iu was injected i.v. If required, additional doses of thiopentone 1 mg kg^{-1}, fentanyl 0.5 μg kg^{-1}, buprenorphine 1.5 μg kg^{-1} or vecuronium 30 μg kg^{-1} were administered.

The following measurements were undertaken just before the induction of anaesthesia and 15, 30, 45, 60 and 120 min after the end of anaesthesia: *critical flicker fusion frequency* (CFF-threshold) (Smith and Misiak, 1976); *relaxation of ocular muscles* with Maddox wing apparatus (Hannington-Kiff, 1970a, b); *subjective sedation*: quite alert to extremely tired; *analgesia*: no pain to very severe pain; *nausea*: none to vomiting. (The last three assessments by 10-cm visual analogue scales marked 0–10 (Bond and Lader, 1974; Maxwell, 1978).) In addition, as a reference, in order to test the postoperative state of the patients, the postanaesthetic recovery score was recorded by the anaesthesist in the recovery room by evaluating muscle activity, ventilation, circulation, consciousness and skin colour (maximum 10 points (Aldrete and Kroulik, 1970)). Heart rate, and systolic and diastolic arterial pressures (sphygmomanometer) were monitored as depicted in figure 1. The expiratory end-tidal carbon dioxide was monitored during anaesthesia (Datex, Normocap, Espoo, Finland) and maintained at 5±0.5% to maintain normoventilation. The degree of neuromuscular blockade was assessed by observing movements of the fingers following four successive supramaximal stimuli administered to the ulnar nerve near the wrist via surface electrodes at a frequency of 2 Hz (Myotest, Biometer, Odense, Denmark). An additional dose of vecuronium was administered when a weak but still visible twitch from the second stimulus was observed. Extubation of the trachea was performed when all four twitches were seen with no or only slight fade, and when the end-tidal carbon dioxide concentration remained less than 7% while the patients were breathing spontaneously (Salmenperä and Tammisto, 1980). During the anaesthesia, lactated Ringer's solution (without glucose) was infused—approximately 1000 ml followed by Normosol-type infusion of 1000 ml. In no patient was the estimated blood loss more than 500–600 ml. If required, in the recovery area, buprenorphine 4 μg kg^{-1} was injected i.m. for severe pain.

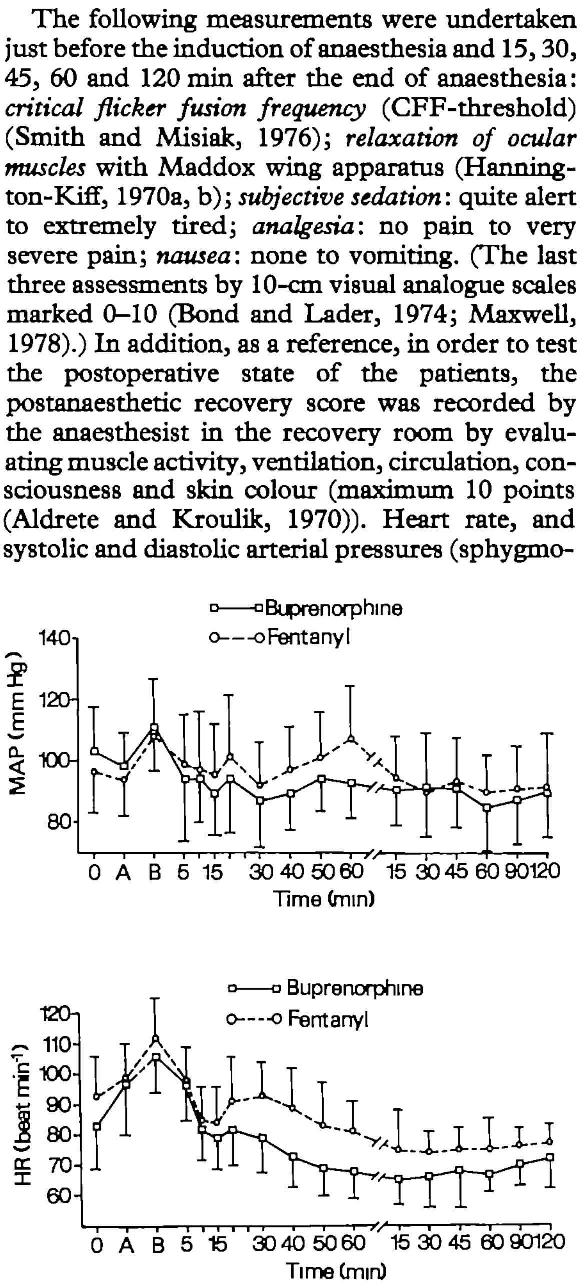

FIG. 1. Changes (mean ± SD) in mean arterial pressure (MAP) (mm Hg) and heart rate (HR) (beat min^{-1}) during anaesthesia and in the recovery room. A = Before intubation; B = after intubation.

Normally distributed data were analysed using Student's *t* test and two way ANOVA (Cohen and Holliday, 1982) with repeated measures on one factor. On the ordinal data Mann–Whitney *U* test (Glantz, 1981) and Chi-square test were used.

RESULTS

The two groups were comparable in respect to age, weight, height, ASA classification, induction–delivery time, intubation time and the duration of anaesthesia: there were no significant differences (table I). All newborns had Apgar scores ⩾ 7. During anaesthesia only two of the patients in the buprenorphine group needed a single additional dose of vecuronium, compared with 12 patients in the fentanyl group ($P = 0.0035$). There were no significant differences between the two groups in the cardiovascular variables (mean arterial pressure, heart rate), but there were similar, statistically significant time-related changes ($P < 0.001$) in both groups during anaesthesia and in the recovery period (fig. 1, table II), but neither drug had any significant influence on these variables. In the recovery room six of the 15 patients in the fentanyl group asked for an

TABLE I. *Comparison of the two study groups. The values are mean ± SD. Probability tested by Student's* t *test (non-paired data) and † Chi-square test*

	Fentanyl group	Buprenorphine group	*P*
No. patients	15	15	ns
Age (yr)	31.1 ± 6.3	29.8 ± 6.4	ns
Weight (kg)	75.2 ± 12.9	79.5 ± 18.7	ns
Height (cm)	162.4 ± 5.8	162.9 ± 5.9	ns
ASA class I	13	14	ns
class II	2	1	ns
Induction–delivery time (min)	4.6 ± 1.0	4.0 ± 0.8	ns
Intubation time (s)	126.1 ± 20.0	118.2 ± 21.5	ns
Duration of anaesthesia (min)	58.1 ± 7.6	58.1 ± 7.7	ns
Patients needing additional neuromuscular blocker	12/15	2/15	*P* = 0.0035†
Patients needing analgesic in the recovery room	6/15	0/15	*P* = 0.022†

TABLE II. F*-values and probability levels using two-way analysis of variance (ANOVA) with repeated measures on one factor (time)*

	Factor 1 = drug	Factor 2 = time	Interaction
Heart rate	0.977	30.85	0.926
P	0.66	< 0.001***	0.54
Arterial pressure	0.950	9.33	0.126
P	0.66	< 0.001***	0.99

additional analgesic (buprenorphine $4\ \mu g\ kg^{-1}$ i.m.) from 30 to 95 min (mean 61 min) after the end of anaesthesia. Values of the postoperative measurements, however, did not differ statistically from those of the other patients in the fentanyl group and, therefore, the results of the 15 patients of this group were combined.

In the CFF-threshold test the patients showed a wide inter-individual variation in preanaesthetic values and no statistically significant differences in the absolute values were found between the two groups in the recovery period (table III). The CFF-readings did not reach the pre-anaesthetic values during the 2-h study period in either group. When results were expressed as relative changes in CFF-threshold, the buprenorphine group showed a statistically significantly ($P = 0.027$) lower value at 90 min (table III).

The measurements with Maddox wing apparatus showed evidence of more rapid recovery in the fentanyl group. The difference between the two study groups increased significantly from 30 min to 120 min (table III). However, no statistically significant differences were found in the PARS values (table III).

Results of subjective expressions of postoperative sedation, pain and nausea (measured by visual analogue scales) are summarized in table III. Following the equal maximum values of sedation at 15 min after surgery, the patients in the fentanyl group showed a more rapid recovery with significant differences at 60 and 90 min. At 120 min the difference did not reach statistical significance.

The most striking difference between the two groups was found in subjective pain rating (table III). In both groups the scores stayed at a relatively constant value (variation in means from 7.1 to 5.1 for the fentanyl group and from 3.4 to 3.9 for the buprenorphine group). Patients in the fentanyl group expressed markedly higher scores at every time point in the postoperative period (*P* values from 0.001 to 0.003, table III). There were no differences between the two groups in nausea scores, although two patients in the buprenorphine group vomited (table III).

TABLE III. *The postanaesthetic recovery of the patients measured with both objective methods (CFF, ΔCFF, Maddox wing, postanaesthetic recovery score (PARS)) and subjective methods (visual analogue scale (VAS) for sedation, pain and nausea). Mann–Whitney* U *test, mean ± SD*

	Before anaesth.	15 min	30 min	45 min	60 min	90 min	120 min
CFF (Hz)							
Fentanyl	30.2±2	24.4±3.2	25.1±2.8	26.1±2.9	26.4±3.1	27.3±3.1	27.6±2.9
Buprenorphine	32.0±2.6	25.7±3	26.6±3.4	26.9±3.5	26.9±3.2	27.1±2.9	28.5±3.1
	$P = 0.02$	ns	ns	ns	ns	ns	ns
CFF relat. (Δ Hz)							
Fentanyl	0	5.8±2.6	5.1±2.4	4.1±2.4	3.8±2.6	2.9±2.4	2.6±2
Buprenorphine	0	6.3±3.7	5.8±3.4	5.4±3.4	5.2±3.1	4.9±2.9	3.5±2.8
	ns	ns	ns	ns	ns	$P = 0.027$	ns
Maddox wing (d)							
Fentanyl	1.7±2.4	16.4±4.7	13.3±5.1	10.9±4.3	9.1±5.3	7.1±4.7	4.9±4.1
Buprenorphine	2±2.4	17.9±5.6	16.3±5.9	15±5.3	14.1±6.4	12.5±5	10.5±4.9
	ns	ns	$P = 0.03$	$P = 0.02$	$P = 0.02$	$P = 0.04$	$P = 0.001$
PARS (points)							
Fentanyl	10±0	8.8±0.5	9.3±0.6	9.6±0.4	9.8±0.4	9.9±0.3	9.9±0.3
Buprenorphine	10±0	8.3±1.0	8.9±1.0	9.3±0.9	9.5±0.8	9.7±0.6	9.9±0.4
	ns	ns	ns	ns	ns	ns	ns
VAS (cm)							
Sedation							
Fentanyl	1.3±1.4	7.7±2	6.2±2	5.3±1.8	4.5±2.3	3.9±2.2	4.2±1.8
Buprenorphine	1.1±1.3	7.7±1.8	6.8±1.9	6.1±1.9	5.9±1.6	5.4±1.9	5.0±1.3
	ns	ns	ns	ns	$P = 0.02$	$P = 0.03$	ns
Pain							
Fentanyl	0.4±0.7	7.1±2.3	6.9±1.9	7.0±1.8	6.9±2	6.4±1.8	5.1±1.8
Buprenorphine	0.1±0.4	3.4±1.6	3.8±1.7	3.9±2	3.7±2	3.4±1.8	3.4±1.7
	ns	$P = 0.0001$	$P = 0.0002$	$P = 0.0001$	$P = 0.0001$	$P = 0.0002$	$P = 0.003$
Nausea							
Fentanyl	0.3±0.7	1.2±1.6	1.1±1.5	0.7±1.3	0.5±0.9	0.3±0.6	0.1±0.4
Buprenorphine	0±0	1.2±3.2	0.5±1.5	1.3±2.9	0.4±1.5	1.3±0.3	0.7±1.5
	ns	ns	ns	ns	ns	ns	ns

DISCUSSION

The measurement of the balance of the extraocular muscles with a Maddox wing apparatus has been shown to be a very sensitive indicator of the rate of recovery from general anaesthesia (Hannington-Kiff, 1970a), and in differentiating between the changes associated with i.v. or inhalation agents (Hannington-Kiff, 1970b). However, in the assessment of changes in CNS arousal produced by a variety of psychotropic (Smith and Misiak, 1976; Hindmarch, 1980) and anaesthetic (Hovorka, Lehtinen and Kalli, 1983) agents, the critical flicker fusion threshold test has been used more widely. Currently, the visual analogue scale is, apparently, the most widely used method with which to rate different subjective sensations of psychoactive agents (Bond and Lader, 1974; Maxwell, 1978; Hindmarch, 1980) with good reproducibility (Revill et al., 1976) especially if numerical scales are used (Downie et al., 1978; Kremer, Atkinson and Ignelzi, 1981). In the present study we compared the usefulness of these three simple devices with that of the postanaesthetic recovery score (Aldrete and Kroulik, 1970) in evaluating the difference in the rate of recovery after the technique of general anaesthesia described above.

We found the Maddox wing apparatus and the visual analogue scale to be the most sensitive tests. Their usefulness became most evident in the late recovery states, once patients had achieved normal postanaesthetic recovery scores. The latter method, and the critical flicker fusion threshold method, appeared to be too insensitive in differentiating between the residual effects of the analgesics used during the anaesthetic.

Apparently, the residual extraocular muscle imbalance after anaesthesia is not only the result of the use of neuromuscular blocking agents, but is also influenced by peroperative analgesics. In the fentanyl group the divergence of the eyes decreased significantly more rapidly, but neither group had attained the preanaesthetic reference value by 2 h after operation. The critical flicker fusion threshold test showed poor sensitivity in distinguishing between the residual effects of the two opioids. A wide inter-individual variation persisted throughout the whole study period and, even when these values were expressed as individual relative changes, no differences were found between the two patient groups, with the exception of slightly higher values for buprenorphine 90 min after anaesthesia. Thus, this method seems to be almost as insensitive as the postanaesthetic recovery score in determining the residual effects of opioids administered during anaesthesia. Improving the accuracy of CFF-measurement by fixing the pupil size with special eye-glasses might be helpful, but this is impossible in the recovery room environment.

Visual analogue scales proved to be valid in evaluating the subjective sensations of pain, sedation and nausea. Pain scales were significantly greater in the fentanyl group during the 2-h study period in the recovery room, which confirms the previously known durations of action of these two analgesics (Kay, 1980). In addition to this, the administration i.m. of buprenorphine to six patients in the fentanyl group should be taken into consideration. As expected, buprenorphine caused more postoperative sedation than fentanyl (Heel et al., 1979; Sjövall, 1983).

The insignificantly greater mean values of heart rate and mean arterial pressure during and after anaesthesia in patients receiving fentanyl are apparently attributable to the shorter analgesic action of this agent.

Surprisingly, nausea and vomiting occurred infrequently in both groups, and were not associated with the longer duration of action of buprenorphine.

The requirement for additional neuromuscular blocker during anaesthesia was decreased in the patients receiving buprenorphine. This finding confirms the previous studies with this long-acting analgesic (Sjövall, 1983).

In conclusion, the Maddox wing apparatus appears to be a useful clinical test with which to evaluate the residual postanaesthetic effects of opioids. It is much more sensitive than the traditionally used postanaesthetic recovery score and the less-used critical flicker fusion threshold method. However, the simplest device, the visual analogue scale, proved to be sensitive as well.

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ELECTRICAL AND MECHANICAL RESPONSES AFTER NEUROMUSCULAR BLOCKADE WITH VECURONIUM, AND SUBSEQUENT ANTAGONISM WITH NEOSTIGMINE OR EDROPHONIUM

B. A. ASTLEY, R. L. KATZ AND J. P. PAYNE

SUMMARY

Six unpremedicated patients who had given their informed consent were given vecuronium 0.08 mg kg^{-1} before elective surgery. Recovery from neuromuscular blockade was measured electrically and mechanically. Neuromuscular blockade was antagonized 1 h after the administration of vecuronium with two doses of neostigmine 2.5 mg (three patients) or edrophonium 0.5 mg kg^{-1} (three patients). Although the onset of initial recovery was similar, subsequent recovery was faster when measured electrically (EMG) than when measured mechanically. Recovery appeared to be faster in younger patients. Reintroduction of neuromuscular blockade occurred after the second dose of neostigmine 2.5 mg, given to antagonize the block. This did not occur after either dose of edrophonium 0.5 mg kg^{-1}.

Vecuronium, a monoquaternary analogue of pancuronium, produces a competitive type of neuromuscular blockade that is said to be mainly post-junctional in character (Baird, Bowman and Kerr, 1982). The drug has been shown to have a more rapid onset, and shorter duration, of action than pancuronium (Agoston et al., 1980; Crul and Booij, 1980; Fahey et al., 1981), and to provide rapid intubating conditions with ease of reversibility. In doses used clinically it is devoid of cardiovascular side effects (Marshall et al., 1980). This study has investigated the recovery of neuromuscular function after the administration of vecuronium by means of simultaneous recordings of electrical and mechanical responses to ulnar nerve stimulation, and the subsequent antagonism of neuromuscular blockade with either neostigmine or edrophonium.

PATIENTS AND METHODS

Six unpremedicated patients about to undergo elective urological surgery gave their informed consent to participate in the study. The patients were fit and of average age (49.2 yr; range 24–70 yr). Premedication was omitted and the anaesthetic sequence standardized in the following way. Anaesthesia was induced with 5% thiopentone 400–600 mg given i.v. and maintained with 60–66% nitrous oxide in oxygen, supplemented by 0.5% halothane, with increments of fentanyl 50 µg as necessary. Heart rate and rhythm were monitored continuously (ECG) throughout each study. A polyethylene cannula was inserted to a radial artery at the wrist to allow the continuous measurement of arterial pressure. Simultaneous recordings were made of both the tetanic and train-of-four responses (measured mechanically) of the adductor pollicis muscle elicited by supramaximal stimulation of each ulnar nerve every 12 s, one with tetanic bursts of 50 Hz for 1 s and the other with trains of stimuli at 2 Hz for 2 s. The train-of-four responses were also measured electrically. After control recordings had been obtained, tracheal intubation was performed after the administration of vecuronium

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0.08 mg kg^{-1} i.v., and artificial ventilation was commenced. The artificial ventilation was continued until the reappearance of the tetanic response, after which it was discontinued and the patient allowed to breathe spontaneously. The times of return of the electrical and mechanical responses were noted. The duration of clinical relaxation was measured from the time of injection of vecuronium to 25% recovery of the first twitch of the train-of-four response (T1). The recovery time was measured as the time taken to recover from 25% to 75% of T1. The duration of action was measured as the time taken to achieve 90% recovery of T1 from the time of injection of vecuronium before the administration of anticholinesterase. At about 60 min after the injection of vecuronium, antagonism of residual blockade was effected with either edrophonium 0.5 mg kg^{-1} or neostigmine 2.5 mg, preceded by atropine 1.2 mg. Results are expressed as means ± SEM.

RESULTS

Onset of block of tetanus occurred at a mean time of 1.31 ± 0.16 min from injection of vecuronium, blockade of all four twitch responses measured electrically occurred at 1.6 ± 0.55 min and blockade of the four twitch responses measured mechanically occurred at 2.17 ± 0.17 min. Minimal fade of the tetanus was noticed during the onset of block. These results are shown in table I. Intubation was performed at 2.86 ± 0.17 min after the injection of the drug.

TABLE I. *Onset of neuromuscular blockade*

Patients	Complete block of tetanus (min)	Complete block of T1(mech.) (min)	Complete block of T1(EMG) (min)
1	1.0	2.0	1.5
2	1.5	2.0	1.5
3	1.0	2.0	1.67
4	1.33	2.0	1.5
5	2.0	3.0	1.67
6	1.0	2.0	1.83
Mean	1.3	2.2	1.6
± SEM	±0.2	±0.2	±0.6

The times of initial return of the various responses are shown in table II. The tetanic response reappeared at 24 ± 2.68 min, and tetanic fade began to recover at 36 ± 2.78 min. The first twitch in the train-of-four (T1) returned at 22.33 ± 2.14 min measured mechanically and 25.5 ± 2.59 min measured electrically. The fourth twitch in the train of four (T4) returned at 33.33 ± 3.42 min (mechanical) and 37.5 ± 3.76 (EMG). All measurements were taken from the time of injection of vecuronium. Artificial ventilation was discontinued at 25.5 ± 2.9 min and spontaneous breathing returned at 28.5 ± 3.0 min after the administration of vecuronium.

Table III shows the duration of clinical relaxation, the recovery time and duration of action of T1. The duration of clinical relaxation was 31 ± 2.5 min measured mechanically and 32.2 ± 4.2 min measured electrically (EMG). These were very similar. However, recovery time of the first twitch of the train of four was 23 ± 6.0 min measured mechanically, but only 12.16 ± 4.1 min measured electrically. Statistical analysis (paired *t* test) showed these results to be significantly different ($P = 0.019$). From table III it can be seen that two of the electrically recorded results were extremely fast, with values less than 4 min. The duration of action was 62.5 ± 9.3 min measured mechanically. Three patients had recovered to > 90% of the control twitch height at

TABLE II. *Initial recovery of neuromuscular function*

	Reappearance of					
Patients	Tetanus (min)	Tetanic fade (min)	T1 (mech.) (min)	T4 (mech.) (min)	T1 (EMG) (min)	T4 (EMG) (min)
1	34	46	30	46	33	47
2	16	31	16	24	18	27
3	24	35	25	37	33	49
4	18	27	18	28	22	32
5	28	41	25	38	26	40
6	24	36	20	27	21	30
Mean	24	36	22.33	33.33	25.5	37.5
± SEM	±2.7	±2.8	±2.1	±3.4	±2.6	±3.8

TABLE III. *Duration of action*

	Time for 0–25% recovery of T1 (min)		Time for 25–75% recovery of T1 (min)		Time to 90% recovery of T1 (min)	
Patients	Mechanical	EMG	Mechanical	EMG	Mechanical	EMG
1	40	42	37	28	90	77.5
2	24	21.5	13	3.5	44	26
3	34	47	15	12	53	63
4	28	25	16	7	47	34
5	34	33	46	20	93	70
6	26	24.5	11	2.5	48	28
Mean	31	32.2	23	12.2	62.5	49.8
±SEM	±2.5	±4.2	±6.0	±4.1	±9.3	±9.4

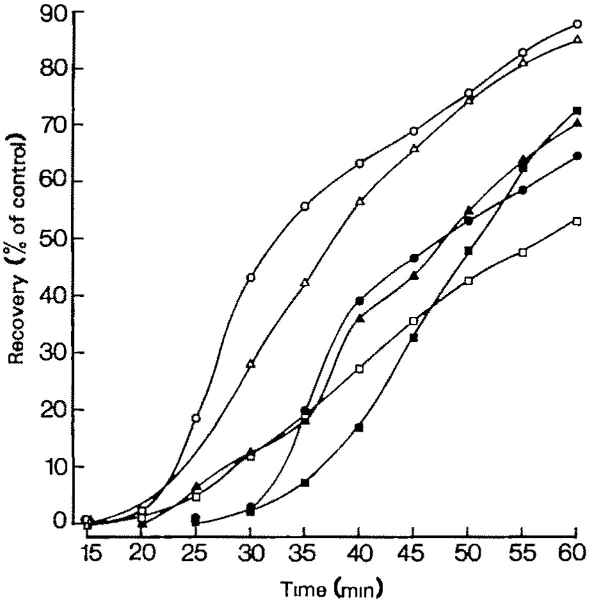

FIG. 1. Recovery of tetanic height (□), tetanic tension ratio (■), amplitude (△ = mechanical, ○ = electrical) and ratio (▲ = mechanical, ● = electrical) of train-of-four responses after neuromuscular blockade with vecuronium.

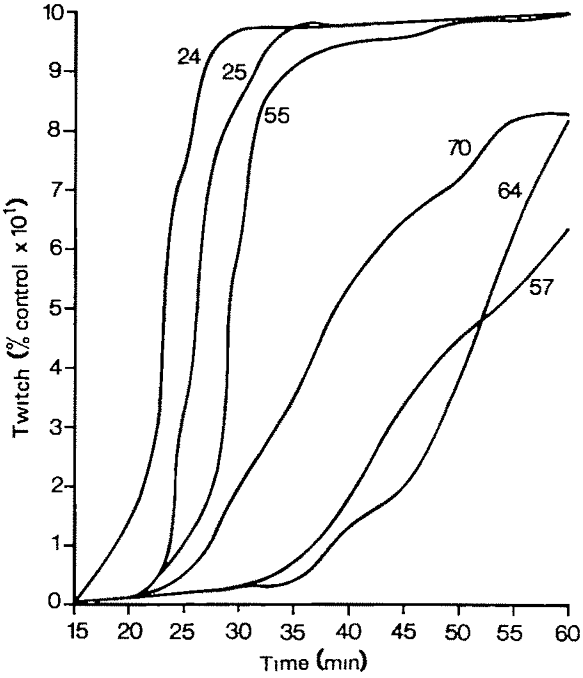

FIG. 2. Recovery of T1 recorded electrically (EMG). The patient's age (yr) is indicated on each curve. Recovery appears to be faster in younger patients.

the time of antagonism of blockade and the remaining values were obtained by extrapolation. The duration of action measured electrically was 49.8±9.4 min. Five patients had recovered to >90% of the control height at the time of antagonism, and the sixth was deduced by extrapolation. The duration of action of the first twitch of the train-of-four measured electrically was significantly shorter than the duration of action of T1 measured mechanically ($P = 0.045$).

In order to give an overall idea of the pattern of recovery, the recovery of the various responses measured were plotted against time (fig. 1). The recovery of the peak height of T1 measured electrically recovered faster than the peak height of T1 measured mechanically, and both were considerably faster than the recovery of the peak height of the tetanic response. Recovery of the ratio of the train-of-four (T4:T1), measured electrically and mechanically, followed a course very similar to that of the recovery of tetanic fade. In figure 1 the sustained tetanic height expressed as a percentage of the peak amplitude, the tetanic tension ratio, was plotted so that the recovery curve followed the same direction. In this study the recovery of the amplitude of the tetanic response was the slowest response to recover.

There was an impression that the rate of recovery was influenced by the age of the patient so the recoveries of the amplitudes of the mechanical and electrical train-of-four responses were plotted against time for each patient, with the age of the patient indicated on each curve. Figure 2 shows the recovery of EMG plotted against time. The youngest patients had more rapid recoveries, and in one patient the recovery time was 2.5 min (table III). Figure 3 shows the mechanical responses plotted against time and, again, the most rapid recovery rates were associated with the youngest patients.

Neuromuscular blockade was antagonized with either neostigmine 2.5 mg (three patients) or edrophonium 0.5 mg kg^{-1} (three patients), preceded by atropine 1.2 mg given at 57 ± 3.4 min after the administration of vecuronium. At this time the tetanic response had recovered to about 50 % of its control height (47.8 ± 7.3 % of control) with 32 % fade. The amplitude of the twitch response measured mechanically was 80.2 ± 7.8 % of control, and 89.2 ± 5.4 % of control measured electrically.

Following the first dose of the reversal agent, 90 % of control tetanic height was achieved in less than 1 min in all patients, and 90 % of the control twitch height within 2 min in all patients.

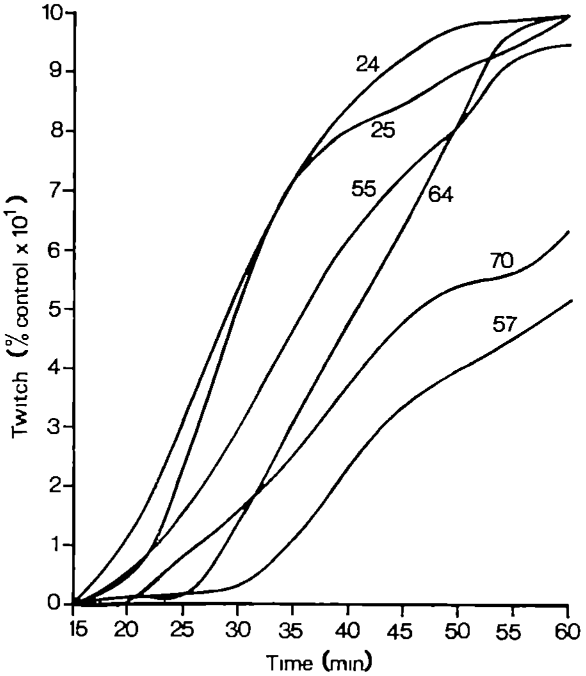

FIG. 3. Recovery of T1 recorded mechanically. The patient's age (yr) is indicated on each curve. Recovery appears to be faster in younger patients.

TABLE IV. *Effect of second dose of neostigmine*

Patient	Tetanic height (% of control)	Tetanic fade (%)	Time to recover to 90 % control tetanic height (min)
1	46	95	24
2	69	93	21
3	76	70	17
Mean ± SEM	63.7 ± 9.1	86 ± 8.0	20.7 ± 2.0

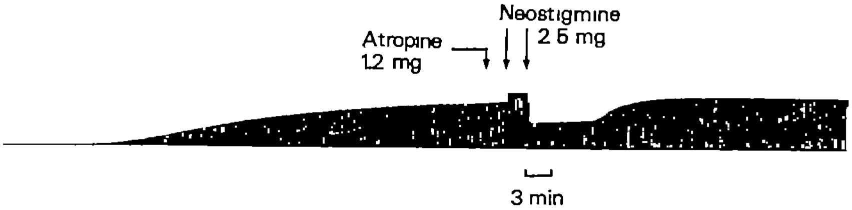

FIG. 4. Tetanic trace from a patient receiving two doses of neostigmine 2.5 mg preceded by atropine 1.2 mg. The first dose restored tetanic height to 95 % of its control value. A second dose given at this point caused marked deterioration in neuromuscular function, with a decrease in amplitude of the tetanic height and development of tetanic fade.

A second dose of the appropriate anticholinesterase was given to study the effect of the reversal agents on patients who had recovered from neuromuscular blockade. The second dose of edrophonium had no effect other than to increase the height of the tetanic response to 92% of control. However, the second dose of neostigmine reintroduced neuromuscular blockade with a decrease in tetanic height and reintroduction of fade in all three patients (table IV). The tetanic height decreased to a mean value 63.7±9.1% of its control height with 86±8.0% fade within 1 min of the administration. This is illustrated in figure 4 which shows a trace of the tetanic response taken from one of the patients in this study. The neuromuscular blockade so produced recovered to 90% of the control tetanic height with no fade in 20.7±2.0 min. This deterioration was not seen on the recording of the train-of-four response.

DISCUSSION

We have compared the onset and recovery of neuromuscular blockade measured mechanically and electrically in a small group of patients. The recovery rates and durations of action of the electrical responses were significantly shorter than those of the mechanical responses. Electromyography measures changes at the neuromuscular endplate, whereas mechanical recordings measure the tension developed, and this depends upon changes in the contractility of the muscle, in addition to changes at the endplate. Various workers have reported differences in the degree of neuromuscular blockade when measurements are made mechanically and electrically (Epstein and Epstein, 1973; Katz, 1973), but not in the time course of recovery. The EMG response is much faster than the mechanical response and the difference in recovery rates is probably the result of some inertia of the muscle response.

In this study the youngest patients showed the most rapid recovery rates following neuromuscular blockade with vecuronium measured both mechanically and electrically. d'Hollander and colleagues (1982) found a significant decrease in the steady state dose requirement and rate of recovery in patients older than 60 yr. Although the numbers in our study are small, the results support this finding.

The duration of action of vecuronium is shorter than that of established neuromuscular blocking drugs (Agoston et al., 1980; Krieg, Crul and Booij, 1980). Despite this faster recovery, at 60 min after the administration of vecuronium in this study the tetanic response had only recovered to about 50% of its control height; antagonism was successfully achieved within 2 min of administration of either neostigmine 2.5 mg or edrophonium 0.5 mg kg^{-1}. Edrophonium has not been widely used as an antagonizing agent in the past because of the belief that the duration of action was considerably shorter than that of other reversal agents, so that antagonism was sometimes incomplete or recurarization occurred (Artusio, Riker and Wescoe, 1950; Doughty and Wyllie, 1952; Nastuk and Alexander, 1954; Katz, 1967; Sugai and Payne, 1975). Some of these reports of unsustained and unreliable reversal may have been the result of inadequate dosage of antagonist or of imprecise monitoring of neuromuscular function. Recent evidence suggests that the duration of action of edrophonium is similar to that of neostigmine (Morris et al., 1981) and it has been shown to be effective in the antagonism of competitive neuromuscular blockade in man (Bevan, 1979; Kopman, 1979; Ferguson, Egerszegi and Bevan, 1980; Baird, Bowman and Kerr, 1982). In all these reports large doses of edrophonium were used (0.5–1.4 mg kg^{-1}).

A second dose of neostigmine given to those patients when fully recovered caused a deterioration in neuromuscular function which lasted about 20 min. The administration of neostigmine to a patient who has almost fully recovered is a common enough situation in the absence of neuromuscular monitoring. This is especially likely when a drug of intermediate duration such as vecuronium is being used. The neuromuscular blocking properties of neostigmine have been known for many years (Briscoe, 1936) and are well documented (Payne, Hughes and Al Azawi, 1980). The failure to demonstrate any deterioration in neuromuscular function following edrophonium under these circumstances is interesting. Just as the competitive neuromuscular blocking agents act at different receptor sites in the neuromuscular junction, so presumably do the anticholinesterase drugs. Hobbiger (1976) has summarized in detail the probable mechanisms by which these agents exert their effects. It is possible that the reversible combination with acetylcholinesterase following edrophonium may lead to a short-lived depolarizing block that was not seen in this study, and under the conditions of this study, edrophonium was a safe agent for antagonism.

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ONSET AND RECOVERY OF ATRACURIUM AND SUXAMETHONIUM-INDUCED NEUROMUSCULAR BLOCKADE WITH SIMULTANEOUS TRAIN-OF-FOUR AND SINGLE TWITCH STIMULATION

M. J. CURRAN, F. DONATI AND D. R. BEVAN

SUMMARY

Single twitch and train-of-four stimulation were applied at 0.08 Hz to each ulnar nerve and the force of contraction of the adductor pollicis was recorded during onset of and recovery from neuromuscular blockade by suxamethonium 1 mg kg^{-1} or atracurium 0.4 mg kg^{-1}. Times to 90% first twitch blockade of train-of-four were (mean ± SEM) 0.82 ± 0.08 and 1.98 ± 0.18 min for suxamethonium and atracurium, respectively, compared with times to 90% single twitch blockade of 1.00 ± 0.07 and 3.35 ± 0.37 min, respectively ($P < 0.05$ *in both cases). Apparent onset time also depended on how long train-of-four stimulation had been applied before injection of atracurium. The mode of stimulation had little effect on time to 10% recovery. The results are consistent with stimulation-induced augmentation in muscle blood flow, which increased delivery of the drug to the neuromuscular junction.*

A rapid onset is a desirable feature of neuromuscular blocking drugs, especially those which are used to facilitate tracheal intubation. The intensity of neuromuscular blockade is monitored most commonly with either single twitch or train-of-four stimulation (Ali, Utting and Gray, 1970; Lee, 1975). The height of the first twitch following train-of-four stimulation is assumed to be the same as with single twitch stimulation, provided the neuromuscular junction is allowed sufficient time (10–12 s) to recover between each train-of-four (Lee, 1975; Lee and Katz, 1980).

Although this assumption might be valid under most circumstances, this may not be so during onset. In animals, rates of stimulation as low as 0.1 Hz applied to peripheral nerves have been found to increase blood flow to the muscles they supply (Saxena, Dhasmana and Prakash, 1983), presumably in response to an increase in metabolic demand. The onset of neuromuscular blockade is, in turn, affected by the rate of delivery of the drug to the receptors, which depends on blood flow (Hennis and Stanski, 1985). It follows that the presence of stimulation might accelerate the onset of neuromuscular blockade, and this acceleration might depend on the frequency of muscle contraction. However, since the adjustment of blood flow in response to the metabolic demands of exercising muscle is not immediate (Honig, 1979), the acceleration of neuromuscular blockade is expected to depend on how long the stimulation has been applied.

The purpose of this study was to determine whether the onset and recovery of neuromuscular blockade were affected by the pattern and duration of stimulation. This was done by comparing the response of both adductor pollicis muscles, each being stimulated with either the train-of-four or single twitch pattern. The patients were given either suxamethonium or atracurium.

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PATIENTS AND METHODS

The design of the study was approved by the Hospital Ethics Committee, and informed consent was obtained from each patient. The study was conducted on 32 ASA class I or II adults (12 male), 18–75 years of age (mean 40 yr, SEM 3) mean weight 70 kg (SEM 3), with no known or suspected hepatic, renal, cardiovascular, pulmonary or neuromuscular disease. The patients were scheduled for surgical procedures during which access to both arms was possible. Premedication consisted of morphine 0.1 mg kg^{-1}, or pethidine 1 mg kg^{-1} and atropine 0.007 mg kg^{-1} i.m., or diazepam 0.1 mg kg^{-1}, 1 h before the scheduled start of the procedure.

On arrival in the operating room, both hands and forearms were immobilized in splints, and each thumb was fixed to a force transducer (Grass FT-10), with a resting tension of 200–300 g. Stimulating electrodes were placed near the ulnar nerves at the elbow. The site of the i.v. cannulation was randomized to the right or left upper extremity. Arterial pressure was monitored with an electronic oscillometer (Dinamap) placed on one leg in order to minimize interference with neuromuscular recordings. The ECG was monitored, and skin temperature was measured over each adductor pollicis muscle.

Anaesthesia was induced with thiopentone 3–5 mg kg^{-1} and fentanyl 1–2 µg kg^{-1}. Ventilation was maintained manually, via a face mask, with 70% nitrous oxide in oxygen, and both ulnar nerves were stimulated supramaximally with square pulses 0.2 ms in duration, delivered by a Grass S88 stimulator through a Grass SIU5 isolation unit. Five minutes after the induction of anaesthesia, atracurium 0.4 mg kg^{-1} or suxamethonium 1 mg kg^{-1} was given within 5 s into a rapidly running i.v. infusion. Tracheal intubation was performed when maximum blockade was attained in both arms, and mechanical ventilation was instituted. Additional doses of fentanyl were administered before intubation and every 20–30 min thereafter.

In 22 patients, single twitch stimulation was applied to one arm every 12 s while train-of-four stimulation (2 Hz for 2 s) was delivered to the other and repeated every 12 s, the selection being made by random allocation. Stimulation was commenced 5 min before the injection of neuromuscular blocking drug and maintained throughout the study. Twelve patients received atracurium 0.4 mg kg^{-1} and 10 suxamethonium 1 mg kg^{-1}. To determine whether the duration of stimulation before administration of the neuromuscular blocker had any effect on onset, train-of-four stimulation was applied to both arms in another 10 patients, but the stimulation was started at the time of the injection of atracurium 0.4 mg kg^{-1} to one arm, and 5 min before in the other. In all patients, neuromuscular monitoring was continued until recovery to 10% twitch height was observed in both arms.

Both single twitch height and the height of the first twitch of the train-of-four were expressed as percentages of pre-injection (control) values. Onset time was defined as time from injection of the myoneural blocking drug to 10% single or first twitch height (or 90% blockade). Similarly, duration was defined as time from injection of the myoneural blocker until 10% twitch height was attained.

The results were expressed as mean values with the standard error as an index of dispersion. Comparisons within groups were performed using Student's paired *t* test. Comparisons between groups were made using Student's unpaired *t* test. Differences were considered significant when $P < 0.05$.

RESULTS

All three groups were comparable with respect to age and weight.

In all patients, the onset of neuromuscular blockade was more rapid in the muscle stimulated with the train-of-four pattern when compared with single twitch (fig. 1). With atracurium, mean time to 90% blockade was 1.98 ± 0.18 min with train-of-four and 3.35 ± 0.37 min with single twitch stimulation ($P = 0.0005$) (fig. 2). With suxamethonium, time to 90% blockade was 0.82 ± 0.08 and 1.00 ± 0.07 min for train-of-four and single twitch, respectively ($P = 0.0004$) (fig. 3).

In all patients, atracurium-induced neuromuscular blockade appeared earlier in the arm which had been subjected to train-of-four stimulation for 5 min before injection compared with the arm in which train-of-four stimulation was commenced at the time of injection of the drug (fig. 4). Time to 90% blockade was 1.65 ± 0.13 min in the previously stimulated arm and 2.80 ± 0.07 min in the unstimulated arm ($P = 0.00015$).

In all patients, neuromuscular recovery of the adductor pollicis muscle which was blocked first

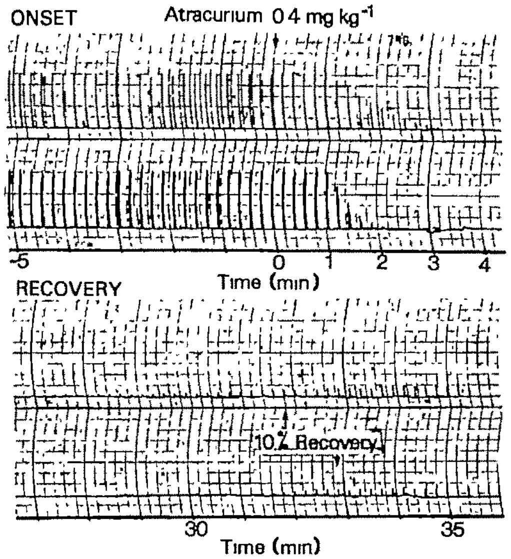

FIG. 1. Simultaneous responses in one patient to single twitch and train-of-four stimulation (top and bottom, respectively, of each strip) during onset of and recovery from neuromuscular blockade. Atracurium was injected at time zero.

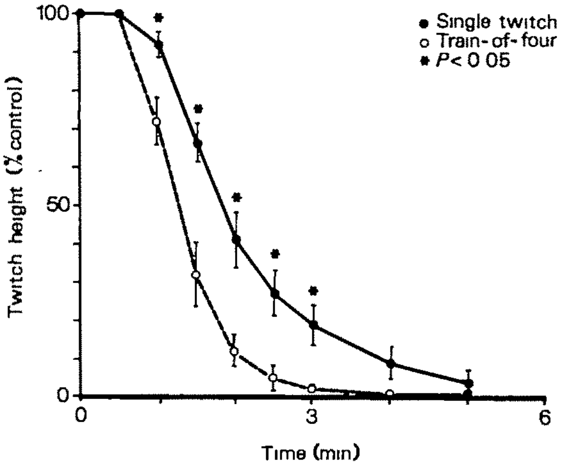

FIG. 2. Mean ($\pm$SEM) single twitch height and train-of-four first twitch height in 12 patients, as a function of time after injection of atracurium 0.4 mg kg^{-1} with train-of-four and single twitch stimulation to each arm, respectively.

occurred last (table I). For atracurium, the muscle stimulated with single twitches recovered 3.7 min ($\pm$0.64; $P = 0.0003$) before the one stimulated with trains-of-four. In the case of suxamethonium, the difference was 1.0 min ($\pm$0.22; $P = 0.0014$). The arm subjected to train-of-four stimulation for 5 min before the injection of atracurium recovered 3.9 min ($\pm$0.8; $P = 0.004$) after the contralateral

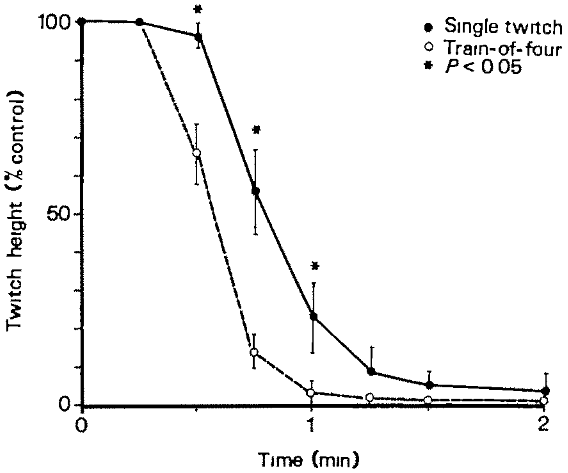

FIG. 3. Mean ($\pm$SEM) single twitch height and train-of-four first twitch height in 10 patients, as a function of time after suxamethonium 1 mg kg^{-1} with train-of-four and single twitch stimulation to each arm, respectively.

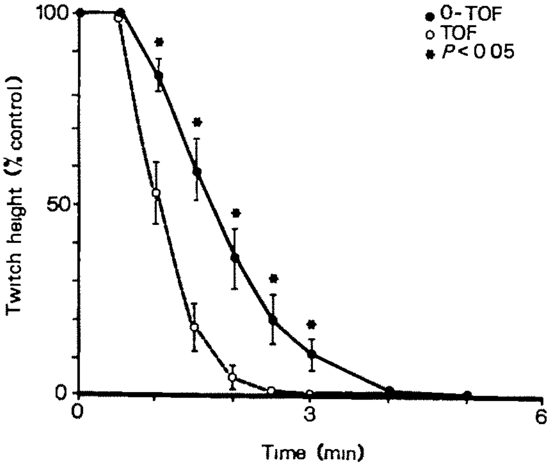

FIG. 4. Mean ($\pm$SEM) train-of-four first twitch height in 10 patients as a function of time after injection of atracurium 0.4 mg kg^{-1}. In one arm, stimulation was started 5 min before atracurium was given (open symbols) and in the other stimulation was started at the time of atracurium injection (closed symbols).

TABLE I. *Time to 10% recovery with single twitch (ST) and train-of-four (TOF) stimulation (mean$\pm$SEM)*

	ST (min)	TOF (min)	P
Atracurium ($n = 12$)	31.2$\pm$1.4	35.0$\pm$1.1	< 0.001
Suxamethonium ($n = 10$)	7.1$\pm$0.5	8.1$\pm$0.5	< 0.005

TABLE II. *Onset and recovery times for atracurium 0.4 mg kg^{-1}, with train-of-four stimulation started at the time of drug injection (0–TOF), and 5 min before (TOF–TOF)* (n = *10*)

Stimulation	Onset time (min ± SEM)	Recovery time (min ± SEM)
TOF–TOF	1.65 ± 0.13	37 0 ± 2.7
0–TOF	2.80 ± 0.07	33.1 ± 2.6
P	< 0.0002	< 0.005

arm, to which train-of-four stimulation was started only when the drug was injected (table II).

There were no detectable differences in the onset of blockade attributable to hand dominance, the site of the i.v. cannulation or skin temperature. Among the 22 patients who received atracurium, train-of-four stimulation was applied to one arm starting 5 min before the injection of the neuromuscular blocker. Of these, 12 were dominant arms. Time to 90% blockade was 1.91 ± 0.18 min in the dominant and 1.72 ± 0.17 min in the non-dominant hand (ns). Similarly, time to 90% blockade was 1.88 ± 0.17 min in the extremity in which the i.v. cannula was sited, and 1.71 ± 0.15 min in the contralateral hand (ns). Skin temperatures in the vicinity of both adductor pollicis muscles was always within 1 °C of each other and usually differed by less than 0.5 °C.

DISCUSSION

This study demonstrated that the apparent onset of neuromuscular blockade in the adductor pollicis muscle depends on the pattern and duration of stimulation. It was more rapid when nerve stimulation was applied more frequently, since four times as many impulses were delivered with train-of-four as with single twitch stimulation. This was found to be true for both atracurium and suxamethonium, two neuromuscular blockers with different mechanisms of action. The onset of action depended also on the duration of the train-of-four stimulation before the administration of the blocking drug. These differences in onset were unrelated to hand dominance, the site of the i.v. infusion or skin temperature. The adductor pollicis which blocked first always recovered last, but the differences were small compared with the duration of action.

Comparison of the simultaneous stimulation of two arms was made by Payne and Hughes (1981) and Hughes and Payne (1983). They administered atracurium to patients who received single twitch stimulation in one arm and tetanic stimulation for 1 s in the other, each pattern being repeated every 12 s. Neuromuscular function disappeared earlier and recovered later with tetanic stimulation than with single twitch. The plasma concentration of atracurium associated with a 50% depression in tetanic response was lower than that corresponding to a 50% depression in single twitch height (Weatherley, Williams and Neill, 1983). However, this cannot be the only explanation for a more rapid onset for tetanic responses, because the biophase rate constant, which describes the rate of entry of the drug to the effect compartment (Hennis and Stanski, 1985), is much more rapid with tetanic stimulation (Weatherley, Williams and Neill, 1983). It follows that a more rapid onset in the muscle to which tetanic stimulation was applied may also be the result of a more rapid delivery of the drug to the neuromuscular junction.

The neuromuscular junction recovers from train-of-four stimulation within 10–12 s (Ali, Utting and Gray, 1970; Lee, 1975; Lee and Katz, 1980). This suggests that the large differences observed between train-of-four and single twitch stimulation in this study were not attributable to a different sensitivity of the neuromuscular junction to both modes of stimulation. Several observations made in this study support this hypothesis. First, a more rapid onset with train-of-four stimulation was also seen with suxamethonium, a depolarizing blocker, which does not have the same mechanism of action as atracurium. Second, if the differences observed were solely the result of a different sensitivity of the neuromuscular junction, the relationship between single twitch blockade and first twitch blockade of the train-of-four should have been the same during onset and during recovery; this was not the case, because the discrepancy between single twitch and train-of-four stimulation was much greater during onset than recovery. Finally, if the neuromuscular junction were more sensitive to the first stimulation in a train-of-four than to single twitch stimulation, apparent onset time would have been independent of how long train-of-four stimulation had been applied.

Access of neuromuscular blocking drugs to the active site depends on tissue perfusion, rate of diffusion of the drug to the receptor, time constant of association to the receptor and the extent of non-specific binding (Hennis and Stanski, 1985).

TABLE III. *Mean onset time (min) of atracurium blockade after a 0.5-mg kg^{-1} dose*

Source	Onset time (min)
Train-of-four stimulation:	
Basta and others (1982)	1.7
Hunter, Jones and Utting (1982)	1.8
Healy and others (1986)	2.3
Single twitch stimulation:	
Gergis and others (1983)	4.1
Foldes and others (1983)	5.7
Ramsay and others (1984)	2.8

Of these, tissue perfusion, or blood flow to the neuromuscular junction, appears important. Onset of suxamethonium blockade was delayed in patients with low cardiac output (Harrison and Junius, 1972), and the time to maximum gallamine blockade was inversely dependent on blood flow (Goat et al., 1976). Nerve stimulation at rates as low as 0.1 Hz has been found to increase muscle blood flow five- to six- fold compared with the contralateral limb in animals, and this increase was abolished by paralysing doses of drug (Saxena, Dhasmana and Prakash, 1983). This can be explained by the need for contracting muscle to be supplied with oxygen. Thus, it is reasonable to assume that delivery of drug to muscle was enhanced when train-of-four stimulation was used, because the muscle contracts four times as often as with single twitch stimulation. Similarly, the onset time was shortened if train-of-four stimulation had been established for 5 min, because of the time required for the muscle blood flow to adapt to exercise (Honig, 1979). Once neuromuscular blockade had been established, the muscle no longer required a large blood flow (Saxena, Dhasmana and Prakash, 1983), and the washout of the neuromuscular blocker presumably proceeded at a rate independent of the rate or pattern of stimulation. Thus, the differences in the time to 10% recovery between the two arms were most likely the result of the higher initial concentrations achieved in the arm which had preferential delivery of the drug, whether this was achieved by more frequent stimulation (train-of-four *v.* single twitch), or by prolonged stimulation (train-of-four for 5 min before injection of the drug *v.* at the time of injection).

Quite apart from the exact mechanism for the effect, the findings of this study have some implications regarding the onset of action of neuromuscular blocking drugs. Since the onset time depends on the mode of stimulation and the duration of its application, comparisons should be made only between identical modes of stimulation. For example, measured onset times after a 0.5-mg kg^{-1} bolus dose of atracurium are consistently longer in studies which involved single twitch rather than train-of-four stimulation (table III). Although significant, the differences in recovery times obtained by either mode of stimulation are too small to be of clinical significance. However, because of the large differences observed in the measurement of onset times, it is not clear which mode of stimulation should be used to monitor the onset of action of myoneural blocking drugs. It is expected that neuromuscular blockade will occur later in an unstimulated muscle. Therefore, it would appear safer to use single twitch stimulation at a frequency of no more than 0.1 Hz, which involves less stimulation than the train-of-four pattern. However, the rate of access of the blocking drug to upper airway and respiratory muscles, which must be paralysed if good intubating conditions are desired, might be different from the stimulated or unstimulated adductor pollicis. Thus, adductor pollicis monitoring using single twitch stimulation may be used as a rough guide of the onset of relaxation, but not as an accurate predictor of paralysis in all muscles.

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Br. J. Anaesth. (1987), 59, 995–1003

ATRACURIUM, VECURONIUM AND PANCURONIUM IN END-STAGE RENAL FAILURE

Dose–Response Properties and Interactions with Azathioprine

L. GRAMSTAD

SUMMARY

Dose–response relations for atracurium, vecuronium and pancuronium were determined in patients in end-stage renal failure for the initial neuromuscular blockade (using three cumulative doses) and for the maintenance of stable 90% response (during continuous infusion). All measurements were during renal transplant surgery, and the interaction of azathioprine on neuromuscular blockade was estimated. Mean ED_{95} doses were ($\mu g\ kg^{-1}$): atracurium 375.6, vecuronium 67.2, pancuronium 86.6; the initial blockade required significantly larger doses than in normal patients (37%, 20% and 45%, respectively, using ED_{50} values). Mean infusion rates for 90% sustained blockade in renal failure were ($\mu g\ kg^{-1}\ h^{-1}$): atracurium 409.4, vecuronium 78.3, pancuronium 14.2. The atracurium dose was not influenced by renal function, whereas vecuronium and pancuronium requirements were significantly reduced by 23.2% and 61.5%, respectively, compared with normal patients (previous study). Azathioprine was injected at the rate of 1 mg kg^{-1} min^{-1} for 3 min at stable 90% neuromuscular blockade with constant-rate infusion of the neuromuscular blocking drug. This produced a relatively small and transient antagonism of blockade—probably of negligible clinical significance.

The pharmocokinetics of the neuromuscular blocking agents atracurium and vecuronium were found to differ little when studied in patients with normal renal function and in those with renal failure (Fahey et al., 1981; Fahey et al., 1984; Bencini et al., 1986). Indeed, both drugs are suitable for use in anephric patients (Hunter, Jones and Utting, 1984). However, the evaluation of these drugs in renal failure requires a knowledge of doses required for the induction, as well as the maintenance, of blockade. In addition, possible interactions with the immunosuppressive agents used commonly in association with renal transplantation require clarification.

In patients with end-stage renal failure we have determined the dose–response relations for initial neuromuscular blockade induced by atracurium, vecuronium or pancuronium, as well as the dose requirements for these drugs during continuous infusion. The design of the study conformed with a previous similar study (Gramstad and Lilleaasen, 1982) and an earlier parallel study (Gramstad and Lilleaasen, 1985), so that we could compare the present results with our previous findings in patients with normal renal function. Interactions with azathioprine were also assessed in the present investigation.

PATIENTS AND METHODS

Thirty patients (nine female) (ASA class III), 18–63 yr, in renal failure and requiring haemodialysis, were investigated during anaesthesia for transplantation of renal grafts from living or cadaver donors. In recipients of living donor grafts, bilateral nephrectomy preceded the transplantation. Informed consent was obtained before the patients were randomized to receive atracurium, vecuronium or pancuronium. Sampling was stratified with respect to sex, as well as the distribution of brain-dead and living donor transplants, because only recipients of living donor grafts were routinely given azathioprine

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before and during the operation. Exclusion criteria were: symptoms of neuropathy (assessed by motor dysfunction or impaired skin sensation in an extremity), other neuromuscular disorders, liver disease, more than 20% deviation from normal weight, peripheral oedema, treatment with aminoglycoside or imidazol antibiotics, preoperative serum calcium concentrations less than 1.9 or greater than 2.9 mmol litre^{-1} (normal 2.2–2.6 mmol litre^{-1}), pre- or peroperative serum potassium concentrations of less than 3 or greater than 6 mmol litre^{-1} (normal 3.8–4.6 mmol litre^{-1}). Patients excluded because their serum potassium concentration exceeded this predetermined range during surgery were replaced by new patients.

Patients receiving living donor grafts were dialysed 48 h before operation. Recipients of a cadaver graft were transplanted irrespective of day of last dialysis, although six patients required a short period of dialysis before operation to correct hyperkalaemia.

Serum electrolyte concentrations and blood-gas tensions were determined within a few hours before the induction of anaesthesia. Preoperative serum concentrations of magnesium and ionized calcium were measured after storage of frozen samples (−70 °C). The Ca^{2+} concentrations were adjusted to pH 7.40 (ICA 1; Radiometer, Copenhagen).

Patients scheduled to receive living donor transplants were given azathioprine 5 mg kg^{-1} by mouth on each of the 2 days preceding operation. Premedication was with diazepam 10 mg by mouth about 2 h before operation. Patients with metabolic acidosis, which might have required correction during the early stage of surgery, were given 4.2% sodium bicarbonate before the induction of anaesthesia.

After the injection of atropine 0.6 mg i.v., anaesthesia was induced with diazepam 15–30 mg, fentanyl 0.1–0.5 mg, and sufficient thiopentone 0–325 mg i.v. to abolish the eyelash reflex. Ventilation was assisted with 100% oxygen via a face mask. The ulnar nerve of the arm without an arteriovenous shunt or fistula was stimulated electrically at the wrist via subcutaneous needle electrodes which were connected to a Myotest nerve stimulator (Biometer, Odense, Denmark) delivering supramaximal impulses at 0.1 Hz. The evoked adduction force of the thumb was measured using a Statham UC3 transducer (with UL4-20 load cell) connected to a Hewlett–Packard 7702B recorder equipped with 8805C amplifier. Resting thumb tension was maintained between 200 and 300 g.

When control twitch height was stable, the appropriate neuromuscular blocking drug was given in a cumulative manner. Pilot studies indicated, however, that a cumulative technique required more time in uraemic patients than in comparative groups of normal patients (previously investigated using four cumulative doses (Gramstad and Lilleaasen, 1982)). Therefore, we gave four equal increments, the two first increments administered in one dose, to produce up to three points on each individual dose–response curve. After the injection of each dose, the twitch response was observed until a maximum effect was obtained, as judged by three consecutive twitches of equal height, before the next dose was given. The total dose was equal to the ED_{95} estimated previously in normal patients using a comparable cumulative technique (Gramstad and Lilleaasen, 1982). The increments were: atracurium 69 μg kg^{-1}, vecuronium 14 μg kg^{-1} and pancuronium 16 μg kg^{-1}.

At maximum effect, and after the last incremental dose, the trachea was intubated. In poor responders, however, an additional dose producing about 90–95% twitch depression was given before intubation. Subsequently, ventilation was controlled mechanically (Servo 900B ventilator). Anaesthesia was maintained with 60–65% nitrous oxide in oxygen, and increments of fentanyl were given as required. The inspired minute volume was adjusted, either to keep end-tidal carbon dioxide concentration between 4 and 5 vol% (Siemens–Elema CO_2 Analyzer 930 connected to the ventilator), or to keep arterial carbon dioxide tension between 4.0 and 5.3 kPa (ABL3 blood gas analyser (Radiometer, Copenhagen)). A heating mattress was used to prevent cooling during operation.

After the maximum effect of the last increment of the neuromuscular blocker had been obtained, the drug was administered by continuous infusion, using a Hoechst PP50 infusion pump. The drug solutions were prepared in physiological saline at 4 °C immediately before anaesthesia. Concentrations of the solutions were chosen so that the 50-ml infusion syringe should not normally have to be replaced during the study. The concentrations were: atracurium 1.8 mg ml^{-1}, vecuronium 0.4 mg ml^{-1} and pancuronium 0.04 mg ml^{-1}.

The rate of infusion was titrated to produce constant 90% twitch depression. After 60 min of neuromuscular blockade the infusion rate was held constant, and the drug requirements and the twitch responses registered. After a subsequent 15-min period with constant-rate infusion, the twitch response was remeasured, and the individual changes in response during the 15-min time interval were noted.

Azathioprine 3 mg kg^{-1} was then administered at the rate of 1 mg kg^{-1} min^{-1}, while the infusion rate of the neuromuscular blocker was held constant. The ensuing maximum interaction and its latency, as well as twitch response 10 min after the end of the azathioprine administration were measured. In patients receiving living donor grafts, prednisolone 100 mg was given subsequently as a bolus injection and the twitch response was registered for a further 15 min. In recipients of cadaver donor grafts, the injection of prednisolone 100 mg preceded the administration of azathioprine by 0.5 min, because of the more rapid surgery in these patients.

Infusions of 0.9% sodium chloride, Ringer's acetate solution and 5% glucose were administered during the recordings. No blood products were given during the period of the study. The investigations were completed in all patients before the administration of frusemide and the declamping of the renal artery.

The observed twitch depressions were probit transformed for statistical evaluation (Finney, 1952) and log transformations were used in the analysis of drug doses. Composite dose–response curves for initial neuromuscular blockade were determined by a weighted variance component analysis of individual regressions. A preliminary test of our infusion and interaction measurements using a goodness-of-fit test (Shapiro and Wilk, 1965) showed that the approximation to a Gaussian distribution was not rejected ($P = 0.05$), therefore parametric statistical tests were used. Differences between groups were analysed by Student's t test when appropriate, or analysis of variance followed by Bonferroni's t test. Differences were considered statistically significant if $P < 0.05$.

RESULTS

Biochemical values and anthropometric data were comparable in the three groups of patients (table I). New patients replaced two patients who were excluded because their preoperative serum potassium concentrations (mmol litre^{-1}) of 5.0 and 5.3

TABLE I. *Anthropometric and biochemical characteristics of the three groups of patients (mean ± SD). Haemoglobin, haematocrit, pH, carbon dioxide and base excess were measured in whole blood; other biochemical measurements were in serum. In patients receiving a short preoperative dialysis to reduce serum potassium concentration, the measurements of electrolytes after dialysis are included, whereas other variables were not remeasured.* *n = 9*: Missing values in one patient (end-tidal* P_{CO_2}*: 4.6 kPa)*

Variables	Drug group Atracurium (n = 10)	 Vecuronium (n = 10)	 Pancuronium (n = 10)	Normal values
Anthropometric data				
Age (yr)	43.5 ± 11.7	46.7 ± 12.0	41.2 ± 14.2	
Weight (kg)	67.2 ± 9.2	65.5 ± 11.5	67.5 ± 10.7	
Body surface area (m^2)	1.80 ± 0.17	1.78 ± 0.20	1.81 ± 0.18	
Preoperative biochemical data				
Haemoglobin (g dl^{-1})	8.3 ± 2.1	8.9 ± 1.3	8.6 ± 2.4	13.2–16.6 (M)
Haematocrit (%)	24.7 ± 5.7	26.0 ± 4.0	25.4 ± 6.8	39–48 (M)
Potassium (mmol litre^{-1})	4.9 ± 0.7	4.7 ± 0.6*	4.7 ± 0.6	3.7–4.6
Ionized Ca^{2+} (mmol litre^{-1})	1.14 ± 0.16	1.29 ± 0.19*	1.15 ± 0.24	1.19–1.30
Magnesium (mmol litre^{-1})	1.1 ± 0.2	1.1 ± 0.1*	1.1 ± 0.1	0.7–1.0
Total protein (g litre^{-1})	70 ± 7	69 ± 5	67 ± 10	63–80
Creatinine (μmol litre^{-1})	857 ± 129	846 ± 117	947 ± 166	71–124 (M)
Urea (mmol litre^{-1})	21.3 ± 4.7	19.6 ± 4.6	24.3 ± 5.2	2.8–7.7 (M)
Biochemical data at constant infusion				
Potassium (mmol litre^{-1})	4.5 ± 0.6	4.8 ± 0.7	4.6 ± 0.6	3.7–4.6
pH	7.41 ± 0.06	7.43 ± 0.05*	7.44 ± 0.06	7.35–7.43
Arterial CO$_2$ (kPa)	4.5 ± 0.3	4.8 ± 0.5*	4.6 ± 0.4	4.7–6.0
Base excess (mmol litre^{-1})	−2.5 ± 3.1	0.1 ± 2.6*	−0.8 ± 3.0	−3–+3

increased to 6.6 during the study. Cadaver grafts were used in 21 patients; nine patients received a graft from a living donor.

Sixteen patients suffered from chronic glomerulonephritis. Other causes of renal failure included chronic pyelonephritis (four), unspecified nephritis (three), diabetic nephropathy (three) and other diseases (four). Nine patients had received frusemide more than 12 h before operation. Half the patients were on treatment with one or more anti-hypertensive drugs (mainly beta-blocking agents and prazosin). The majority were receiving preparations of iron, vitamins and antacids. A retention enema of calcium polystyrene sulphonate 30 g was required before anaesthesia in one patient in the atracurium group and two patients in the vecuronium group.

An earlier parallel study had demonstrated no evidence of a sex difference in sensitivity to neuromuscular blockers (Gramstad and Lilleaasen, 1985). In the present study, preliminary analysis of the interactive effects of azathioprine demonstrated negligible effects on neuromuscular blockade. The stratification factors were, therefore, ignored in the subsequent statistical analysis.

Initial neuromuscular blockade

Individual dose–response curves are shown in figure 1 and the calculated dose–response values are presented in table II. Relative potencies for atracurium, vecuronium and pancuronium were 1:5.5:3.9 (ED_{50}) and 1:5.6:4.3 (ED_{95}). The periods between first and last cumulative doses were (mean ± SD): atracurium 9.0 min ± 0.9, vecu-

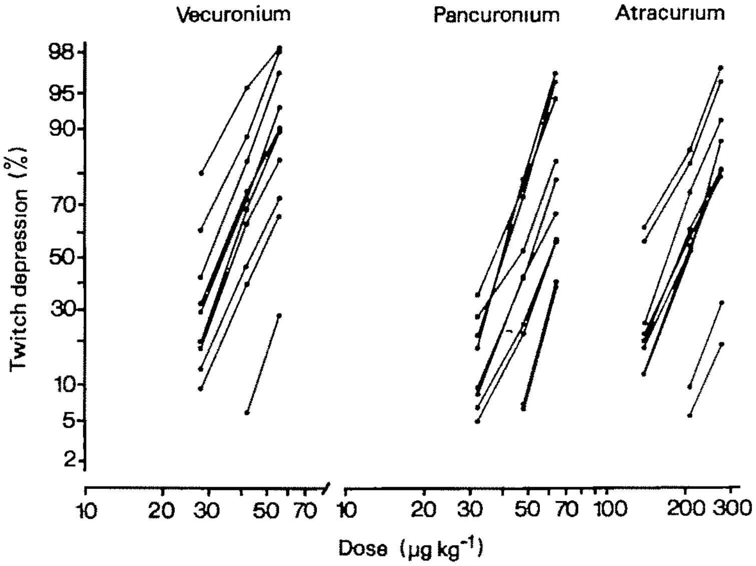

FIG. 1. Individual dose–response relationships. Note: The abscissa is repeated to avoid overlapping curves.

TABLE II. *Calculated mean dose–response values and their 95% confidence limits. Values in patients without renal failure are from a comparable previous study (Gramstad and Lilleaasen, 1982).* *P < *0.02 and* ***P < *0.001 compared with patients with normal renal function*

Drug	ED_{50} ($\mu g\ kg^{-1}$)	ED_{95} ($\mu g\ kg^{-1}$)	Curve slope (Probit $\log^{-1}$)	ED_{50} in normal patients ($\mu g\ kg^{-1}$)
Atracurium	202.5***	375.6	6.13	147.6
	(179.2–228.7)	(279.0–505.8)	(3.51–8.75)	(131.5–165.8)
Vecuronium	36.5*	67.2	6.20	30.3
	(32.0–41.5)	(52.3–86.3)	(3.54–8.87)	(27.7–33.1)
Pancuronium	51.6***	86.6	7.32	35.7
	(46.3–57.4)	(67.9–110.1)	(4.75–9.89)	(33.7–37.7)

ronium 9.3 min ± 0.8, and pancuronium 10.7 min ± 2.0. Table II also shows the ED_{50} values in patients without renal failure, who were investigated similarly in a previous study (Gramstad and Lilleaasen, 1982). The periods between first and last cumulative dose in these latter patients were (mean ± SD): atracurium 9.6 min ± 1.3, vecuronium 9.7 min ± 1.4, and pancuronium 10.4 min ± 2.5. These times are similar to those of the present investigation, making these studies comparable. Our findings show that 20–45 % larger than normal ED_{50} initial doses of the neuromuscular blockers are required in patients with end-stage renal failure (table II).

Infusion administration

Practically stable infusion–response conditions were obtained in all patients before we tested the change in response at constant-rate infusion for 15-min period. Figure 2 shows the distribution of responses at each end of this time interval. The individual changes in response between the beginning and the end of this period were, in absolute values (median with total range in 10^{-2} probits): atracurium 11 (5–20), vecuronium 3 (0–30) and pancuronium 9 (0–14). The drug requirements during the constant rate infusion–response interval are presented in table III. The table shows that the relative potency of atracurium and vecuronium for the maintenance of neuromuscular blockade in end-stage renal failure (1:5.2) approximates the potency ratio observed in relation to the initial neuromuscular blockade. Table III also gives the drug requirements during similar conditions in patients without renal failure, obtained from a parallel study (Gramstad and Lilleaasen, 1985). The present study started about 3 months before, and was completed about 6 months after, the parallel study in normal patients. Dose requirements for sustained 90 % blockade were reduced in end-stage renal failure by 20 % for vecuronium and 57 % for pancuronium. The maintenance dose of atracurium was not markedly influenced by renal function. Two patients were excluded from this latter part of the study: one patient in the pancuronium group

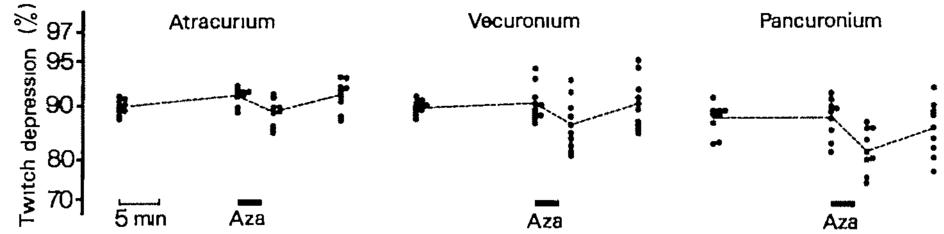

FIG. 2. Distribution of neuromuscular blockade at beginning and end of the 15-min period preceding azathioprine injection, as well as the maximum drug interaction and the remaining blockade 10 min after injection. Minimum degrees of neuromuscular blockade after azathioprine are depicted without specifying individual onsets. Broken lines indicate mean values.

TABLE III. *Dose requirements for the maintenance of sustained 90 % blockade. Comparative values in normal patients are from a parallel study (Gramstad and Lilleaasen, 1985). Mean values and their 95 % confidence limits are quoted.* $^{*}P < 0.05$ *and* $^{***}P < 0.001$ *compared with normal renal function*

		Renal failure			Normal renal function	
Drug	*n*	Dose (μg kg^{-1} h^{-1})	Blockade (%)	*n*	Dose (μg kg^{-1} h^{-1})	Blockade (%)
Atracurium	9	409.4 (339.7–493.2)	91.4 (89.1–92.5)	10	382.8 (331.0–442.7)	89.2 (86.4–90.8)
Vecuronium	10	78.3* (63.4–96.7)	90.5 (87.6–94.5)	9	101.9 (87.4–118.7)	88.6 (84.6–91.4)
Pancuronium	9	14.2*** (9.8–20.6)	88.4 (82.1–91.9)	10	36.9 (31.1–43.7)	90.0 (87.5–91.7)

TABLE IV. *Decrease in neuromuscular blockade after the injection of azathioprine, calculated as change from preinjection values (mean ± SEM). The onset time of maximum antagonism, as well as the 10-min time interval, is measured from the end of injection.* *$P < 0.05$ *between the atracurium and pancuronium groups*

Drug	Maximum decrease in blockade (10^{-2} probits)	Onset of maximum antagonism (min)	Decrease in blockade after 10 min (10^{-2} probits)
Atracurium	13.5 ± 2.7*	1.3 ± 0.1	−0.9 ± 2.6
Vecuronium	17.0 ± 2.7	1.1 ± 0.2	0.0 ± 2.4
Pancuronium	25.9 ± 2.5*	0.9 ± 0.1	8.4 ± 5.3

(brief obstruction of the infusion line) and one patient in the atracurium group (peroperative infusion of cyclosporin, which might have potentiated neuromuscular blockade) (Gramstad et al., 1986)).

Azathioprine interaction

The injection of azathioprine 3 mg kg^{-1} caused a rapid, but small and transient decrease of neuromuscular blockade (fig. 2, table IV). Mean degrees of blockade before the injection of azathioprine, and at maximum antagonism, were: atracurium 91.4–89.1%, vecuronium 90.5–87.3%, and pancuronium 88.4–82.6%. The differences between atracurium and pancuronium reached statistical significance. Ten minutes after the end of the injection of azathioprine, residual interaction was detectable in the pancuronium group only.

In the nine patients receiving living donor grafts, the injection of prednisolone 100 mg 10 min after the administration of the azathioprine produced no apparent change in neuromuscular blockade during a subsequent 11–15-min observation period. To test a possible overall difference in azathioprine interaction between patients with and without prednisolone, the Wilcoxon test statistic for each drug group was calculated (Lehmann, 1975). By addition of χ^2 statistics (Armitage, 1980) the estimated value of P was 0.57.

DISCUSSION

Estimations of the dose–response relations for neuromuscular blocking drugs in patients in renal failure pose particular problems, because the pathophysiological manifestations of the disease are heterogeneous in uraemic patients. Strict criteria for eligibility were, therefore, used to obtain a fairly homogeneous group of patients in relatively uncomplicated end-stage renal failure.

Exclusion criteria which included serum potassium concentrations substantially different from normal were deemed necessary, because it is our experience that the serum potassium concentration may fluctuate considerably during anaesthesia in such patients. For example, in one patient in the pilot study in whom serum potassium concentration decreased to 2.2 mmol from a preoperative value of 3.9 mmol, neuromuscular blockade remained virtually unchanged for about 40 min after the discontinuation of an infusion of pancuronium.

Individual dose–response curves showed great variation in response to the neuromuscular blocking drugs in renal failure. Vecuronium was found to be 5.5–5.6 times more potent than atracurium and 1.4–1.3 times more potent than pancuronium for ED_{50} and ED_{95} doses. These relative doses compare well with our previous findings in normal patients, showing vecuronium to be about 5 times more potent than atracurium and about 1.2 times more potent than pancuronium (Gramstad and Lilleaasen, 1982). However, the absolute dose requirements for the initial induction of neuromuscular blockade were significantly increased in end-stage renal failure—by 37% (atracurium), 20% (vecuronium), and 45% (pancuronium). Since estimations of ED_{95} values are, to a great extent, based on linear extrapolations of dose–response relations, the ED_{50} values were compared rather than the ED_{95} values, even though the latter are more important clinically.

A decrease in the response of atracurium in renal failure was reported recently by Nguyen and colleagues (1985). Using a divided dose of 325 µg kg^{-1} during train-of-four stimulation, these workers found 98% depression of twitch height in normal patients and 93.9% in anephric patients, the latter finding comparing with our ED_{95} value of 375.6 µg kg^{-1}.

Previous investigations have not demonstrated significant differences in responses of vecuronium between patients with normal and those with failure of renal function (Meistelman et al., 1983; Bevan et al., 1984; Orko, Heino and Rosenberg, 1985); although Hunter, Jones and Utting (1984) reported two anephric patients who were highly resistant to vecuronium. Apparent tolerance to vecuronium in renal failure was found by Bencini and colleagues (1986) who measured significantly higher plasma concentrations at 25 and 75% recovery in anephric patients than in patients without renal failure.

To our knowledge, the dose–response relation for pancuronium in patients in renal failure has not been published previously. By using pharmacokinetic–dynamic modelling, Hull and co-workers (1978) demonstrated that patients with total renal failure are likely to be marginally resistant to small doses of pancuronium. These calculations were based on estimated variables by McLeod, Watson and Rawlins (1976), who found that the distribution parameters of pancuronium were altered significantly in renal failure. However, other investigators have not found such differences in the distribution kinetics of pancuronium between patients with normal and failing kidney function (Somogyi, Shanks and Triggs, 1977; Buzello and Agoston, 1978).

As discussed by Feldman (1979), the neuromuscular blocking agent will distribute rapidly into the extracellular water, and the blockade produced will depend on the peak drug concentration in this fluid. The extracellular fluid volume is increased in patients with chronic renal failure requiring regular haemodialysis (Mitch and Wilcox, 1982). In similar patients at our hospital the extracellular fluid volume (sulphate space) was 30.6% larger than normal controls, when measured 48–72 h after dialysis (Fauchald, 1986). Thus such alteration in the distribution of body fluids may increase the dose required for the initial production of neuromuscular blockade in end-stage renal failure. It follows that differences in the estimation of potency, as well as pharmacokinetic measurements, in different studies may depend on the state of hydration of the patients in renal failure. In different units patients may be dialysed to different extents toward their "dry weight" (the minimum weight a patient has achieved without causing symptomatic hypotension).

The biochemical and other characteristics of our patients did not provide any evidence of pharmacodynamic reasons for the lower potencies of the neuromuscular blocking agents in renal failure. However, we could hypothesize that there could be alterations in the plasma concentration–response relations for the three drugs in end-stage renal failure.

Initial doses giving about 90–95% blockade, followed by a continuous infusion titrated to maintain constant 90% response, produced stable neuromuscular blockade at fixed infusion rate within 1 h. This corresponds with the constant infusion–response conditions which pertained in our parallel study in patients with normal renal function (Gramstad and Lilleaasen, 1985). Consequently, the two studies should be directly comparable.

Mean infusion rates for 90% sustained response were (μg kg^{-1} h^{-1}): atracurium 409.4, vecuronium 78.3, and pancuronium 14.2. To our knowledge, infusion dose–response relations for these drugs in renal failure have not been published previously. Compared with the patients with normal renal function, the atracurium requirements were not influenced by the renal failure, whereas the requirements for vecuronium and pancuronium were reduced by 23.2% and 61.5%, respectively.

The clearance of atracurium is not significantly dependent on renal function (Fahey et al., 1984; de Bros et al., 1985), and this supports our finding, because the infusion rate is directly proportional to drug clearance at steady-state. It also accords with the observation of Hunter, Jones and Utting (1982) that dosing intervals for atracurium increments during prolonged neuromuscular blockade were not affected by absence of renal function.

The clearance of vecuronium has not been demonstrated to decrease significantly in renal failure (Fahey et al., 1981; Bencini et al., 1986). Nevertheless, about 20% of the injected dose is excreted in the urine in normal patients (Bencini et al., 1986), which corresponds to the 23.2% reduction in dose requirement for sustained blockade in the renal failure patients. When using repeated increments of vecuronium to maintain neuromuscular blockade in renal failure, Hunter, Jones and Utting (1984) found no difference in dosing intervals in patients with and without renal failure, whereas Bevan and colleagues (1984) reported significantly longer durations of action after repeated doses in renal failure; the latter view accords with our findings.

If we assume steady-state conditions during the constant-rate infusions with pancuronium, the decrease in dosage in renal failure (61.5%) corresponds with other estimates of decreases in plasma clearance as a result of absent renal function: 69.6% (McLeod, Watson and Rawlins, 1976) and 49.8% (Somogyi, Shanks and Triggs, 1977).

The interaction of azathioprine with the three neuromuscular blocking agents was minimal and transient. There was no indication that the interaction was modified by the preinjection of prednisolone; neither did this steroid affect neuromuscular blockade when injected 10 min after azathioprine. The lesser interaction with atracurium than with pancuronium might be explained by the less stable blockade in the former group before the injection of the azathioprine (fig. 2).

Antagonistic effects of azathioprine on non-depolarizing neuromuscular blockade in man and cat were previously reported by Dretchen and co-workers (1976). They showed that neuromuscular blockade with tubocurarine, gallamine or pancuronium in the cat could be completely reversed by the subsequent administration of azathioprine when both drugs were injected to the artery supplying the muscle. The suggested mode of interaction was inhibition of phosphodiesterase by azathioprine, causing increased presynaptic release of acetylcholine. In another study in cats azathioprine 1 or 5 mg kg^{-1} i.v. caused no interaction when injected at maximum blockade after a single bolus dose of atracurium (Chapple, Clark and Hughes, 1983).

These seemingly discrepant findings can probably be explained by the different experimental conditions. Approximated steady-state conditions in our study would provide a more sensitive method than using single bolus injections. When using i.a. injection of the neuromuscular blocker, the concentration gradient from the active site is large after maximum response, and the competitive non-depolarizing drug can rapidly diffuse away when acethylcholine release is facilitated transiently. Measurements during stable blockade in the present study showed minimal interactions, demonstrating that the antagonism produced by azathioprine was clinically negligible during the continuous infusion of neuromuscular blocking drugs.

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Br. J. Anaesth. (1987), **59**, 1004–1010

VECURONIUM AND ATRACURIUM IN PATIENTS WITH END-STAGE RENAL FAILURE

A Comparative Study

J. Y. LEPAGE, M. MALINGE, A. COZIAN, M. PINAUD, Y. BLANLOEIL AND R. SOURON

Vecuronium bromide and atracurium besylate are intermediate-acting competitive neuromuscular blocking agents the elimination of which is, most probably, independent of renal excretion. Previous kinetic and dynamic studies of both drugs, using either a single dose (Fahey et al., 1981a, b; Meistelman et al., 1983; Lebrault et al., 1984) or repetitive administration (Hunter, Jones and Utting, 1982, 1984; Bevan et al., 1984), have highlighted the similarity of responses between patients with end-stage renal failure and patients with normal renal function. Therefore, vecuronium or atracurium have been recommended for patients with altered renal function.

However, the dose–response relationship of atracurium in patients with end-stage renal failure has not yet been reported. Furthermore, the possible differences between the two drugs have not been investigated fully; the sole comparative study in end-stage renal failure (Hunter, Jones and Utting, 1984) failed to find evidence of cumulation of atracurium or vecuronium. However, this study involved non-synchronous groups and neither estimated their potency ratio nor compared the recovery times after repeated administration—aspects which are of great clinical concern during prolonged surgery. The present study was undertaken to assess these points.

SUMMARY

Twenty patients with end-stage renal failure, undergoing kidney transplantation, were assigned randomly to receive either vecuronium or atracurium under evoked twitch tension control. The cumulative-dose technique was used to obtain 95% twitch depression (vecuronium: initial bolus 15 $\mu g\ kg^{-1}$, increments 6 $\mu g\ kg^{-1}$; atracurium: initial bolus 100 $\mu g\ kg^{-1}$, increments 40 $\mu g\ kg^{-1}$). Using ED_{95} values derived from the log–probit dose–response curves, vecuronium was 4.6 times more potent than atracurium. The durations of action of the initial cumulative-doses (from end of injection of the last increment to 25% recovery) were 11.1 ± 3.3 min for vecuronium and 16.2 ± 3.9 min for atracurium ($P < 0.05$). In terms of duration of action of the maintenance doses (vecuronium one-quarter of the total incremental dose; atracurium one-third) some cumulation was observed with vecuronium (interaction time × treatment; cumulation ratio 1.46 ± 0.31 v. 0.98 ± 0.10 for atracurium, $P < 0.001$). After 2 h of surgery, the mean recovery times (25% to 75% twitch height) did not differ (18.5 ± 2.8 min and 16.7 ± 4.4 min). It is concluded that vecuronium might be less safe than atracurium in patients with end-stage renal failure undergoing prolonged operations.

PATIENTS AND METHODS

The investigation was approved by the local Ethics committee and informed consent was given by all patients.

Patients

Twenty patients of either sex, aged between 23–42 yr and undergoing cadaver kidney trans-

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TABLE I. *Demographic and biochemical data (mean ± SEM). No difference between vecuronium and atracurium is significant*

	Vecuronium ($n = 7$)	Atracurium ($n = 9$)
Age (yr)	32.2±3.9	33.1±8
Weight (kg)	58.4±8.4	49.7±5.9
Duration of procedure (min)	141.85±21.48	118.03±16.12
Blood urea (mmol litre^{-1})	16.0±6.2	14.3±6.2
Creatinine clearance (ml min^{-1})	9.7±11.6	3.11±2.1
Sodium (mmol litre^{-1})	136.88±3.71	137.78±1.26
Potassium (mmol litre^{-1})	4.0±0.71	4.20±0.54
Calcium (mmol litre^{-1})	2.43±0.20	2.56±0.13
Magnesium (mmol litre^{-1})	1.02±0.04	0.99±0.02
Haemoglobin (g litre^{-1})	9.6±1.6	9.7±1.9
Albumin (g litre^{-1})	41.23±1.12	40.21±0.98
Total protein (g litre^{-1})	68.43±0.94	69.55±1.02
pH	7.37±0.04	7.37±0.02
Bicarbonate (mmol litre^{-1})	20.75±1.73	20.73±1.63
$P\text{co}_2$ (kPa)	4.40±0.31	4.67±0.44

plantation, were randomly assigned (computer random number program) to two groups of 10 to receive either vecuronium or atracurium. All had been dialysed within 8 h of surgery and were free from cardiac and hepatic dysfunction. There was no previous allergic history. No patient was being treated with calcium or magnesium salts, or enzyme inhibiting or inducing drugs. Four in each group were receiving beta-adrenoceptor blocking agents. No peri-operative antibiotics were given. Table I summarizes the preoperative status of the patients.

Anaesthesia

Premedication was with diazepam 10 mg orally 60 min before the induction of anaesthesia and atropine sulphate 10 µg kg^{-1} i.v. 10 min before anaesthesia was induced with flunitrazepam 20 µg kg^{-1} and fentanyl 10 µg kg^{-1}. Tracheal intubation was performed after spraying the pharynx, larynx and trachea with topical 5% lignocaine. Balanced anaesthesia was maintained with 60% nitrous oxide in oxygen, increments of fentanyl 1 µg kg^{-1} and vecuronium or atracurium as indicated below. Ventilation was controlled throughout so that the end-tidal carbon dioxide concentration was maintained at 5±0.30% (47210 A capnometer, Hewlett–Packard). Oesophageal temperature was kept within the normal range (36.4±0.8 °C).

Assessment of neuromuscular function

The ulnar nerve was stimulated at the wrist using surface electrodes. Ten percent supramaximal pulses were delivered by a 750 Bard Biomedical stimulator at a rate of 0.1 Hz with a duration of 0.2 ms.

The resultant force of adduction of the thumb, as quantified by a force displacement transducer (Statham UC 3 gold cell), was recorded on a polygraph (Monitor V Roche Dassault) (Ali and Savarese, 1976; Stanec, Stanec and Ing, 1983). The sensitivity of the recording system was adjusted to give reliable measurements of 95% twitch depression. The study was divided into two sections.

Section A. The cumulative-dose method was used to determine the potencies of the two neuromuscular blockers. When the twitch height had been stable for at least 10 min, repeated small doses of vecuronium (initial bolus 15 µg kg^{-1}, additional doses 6 µg kg^{-1}), or atracurium (initial bolus 100 µg kg^{-1}, additional doses 40 µg kg^{-1}) were administered i.v. After the injection of each dose the resulting twitch depression was observed until it was maximum,—that is three consecutive twitches of equal height were recorded; the next incremental dose was then given (Donlon, Savarese and Ali, 1974) in order to achieve 95% suppression of the evoked twitch response with careful titration. Patients whose response exceeded this fixed end-point were excluded. The total incremental dose was calculated for each remaining patient. The dose–response curves of each patient and each drug-group were constructed using the log-probit method (Lichtfield, Wilcoxon and Wilcoxon, 1949). Slopes, ED$_{50}$, ED$_{90}$ and ED$_{95}$ values were derived.

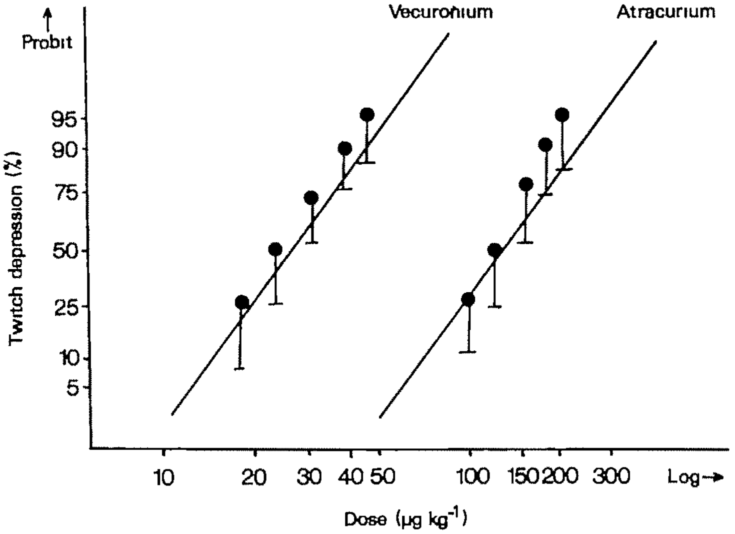

FIG. 1. Dose–response curves for vecuronium and atracurium (mean ± SEM). Vecuronium: $y = -2 + 5.07x$; $r = 0.73$; $n = 35$. Atracurium: $y = 5.75 + 5.23x$; $r = 0.64$; $n = 30$.

Section B. The maintenance doses were one-third of the total incremental dose of atracurium and one-quarter that of vecuronium. They were administered when the twitch had recovered to 25% of control. The variables of time course of neuromuscular blockade were measured: clinical duration of the initial cumulative-dose, from the end of injection of the last incremental dose to 25% twitch recovery (Dur_{25}); durations of maintenance doses, from end of the injection of each maintenance dose to 25% recovery ($\text{Dur}_{\text{rep}\,25}$); recovery time from 25% to 75% recovery after the last maintenance dose (RI). A cumulation ratio for each drug was estimated (duration of the last maintenance dose/duration of the first maintenance dose).

All variables were calculated as mean ± SEM.

Statistical analysis

The patient groups and the slopes of the dose–response curves were compared using Student's *t* tests. The cumulative effect in each drug group was assessed by comparison of the $\text{Dur}_{\text{rep}\,25}$ (two-way analysis of variance followed by a multiple protected *t* test). Statistical differences were considered significant when $P < 0.05$ (two-tailed tests).

RESULTS

The demographic and biochemical data of the patients are summarized in table I. There were no significant differences between the two groups.

Section A

The twitch response was completely suppressed in four patients (three vecuronium, one atracurium); they were excluded from further analysis. Between two and eight incremental doses were required over 6.2 ± 3.1 min to obtain 95% twitch depression in all the patients in the study.

The log–probit dose–response curves are shown in figure 1. Their slopes did not differ and the figures for ED_{50}, ED_{90} and ED_{95} obtained from the curves (table II) were 23.1 μg kg⁻¹, 37.9 μg kg⁻¹ and 43.8 μg kg⁻¹, respectively, for vecuronium and 123 μg kg⁻¹, 181 μg kg⁻¹ and 202 μg kg⁻¹, respectively, for atracurium. If it is assumed that the ED_{95} dose will provide suitable muscle relaxation, vecuronium was 4.6 times as potent as atracurium.

Section B

The largest doses required to maintain at least 75% blockade in procedures lasting about 2 h (table I) were 0.18 mg kg⁻¹ of vecuronium and 1.8 mg kg⁻¹ of atracurium.

TABLE II. *ED_{50}, ED_{90} and ED_{95} for vecuronium and atracurium (mean ± SEM)*

	Vecuronium ($n = 7$)	Atracurium ($n = 9$)
ED_{50} (μg kg⁻¹)	23.1 ± 6.9	123 ± 27
ED_{90} (μg kg⁻¹)	37.9 ± 9.9	181 ± 47
ED_{95} (μg kg⁻¹)	43.8 ± 11.1	202 ± 55

TABLE III. *Dur$_{25}$, RI and cumulation ratio (mean ± SEM). †Last maintenance dose/first maintenance dose*

	Vecuronium ($n = 7$)	Atracurium ($n = 9$)	P
Dur$_{25}$ (min)	11.13±3.30	16.18±3.89	< 0.05
RI$_{25-75}$ (min)	18.50±2.79	16.66±4.04	ns
Cumulation ratio†	1.46±0.31	0.98±0.10	< 0.001

Table III shows the Dur$_{25}$, RI and cumulation ratios. When the first equipotent repeat doses were given, vecuronium appeared to be shorter-acting than atracurium ($P < 0.05$), but after further administration its cumulation ratio was significantly greater ($P < 0.001$), while the mean RI in the two groups did not differ.

The crossing of the Dur$_{\text{rep } 25}$ curves (fig. 2) emphasizes a time × treatment interaction. Although there was a progressive decrease in the numbers of patients concerned with the reinjections, the variabilities of the responses in the two groups were quite similar. However, it is noticeable that the change in the Dur$_{\text{rep } 25}$ in the atracurium group was not statistically significant, although it was so in the vecuronium group. The duration of the seventh dose was one and a half times that of the first one.

DISCUSSION

A number of aspects of the methodology of this study require comment. Flunitrazepam (a long acting benzodiazepine, extensively degraded by the liver) was used in order to avoid halogenated inhalation agents, which have been shown to enhance the effects of vecuronium and atracurium (Rupp, Miller and Gencarelli, 1984; Rupp, McChristian and Miller, 1984). All benzodiazepines, by an action on spinal neurones, have a muscle relaxant effect, that of diazepam being considered to be maximum and that of flunitrazepam to be intermediate (Dantlo et al., 1984). Diazepam has been shown not to interact with competitive neuromuscular blocking drugs (Asbury et al., 1981; McIndewar and Marshall,

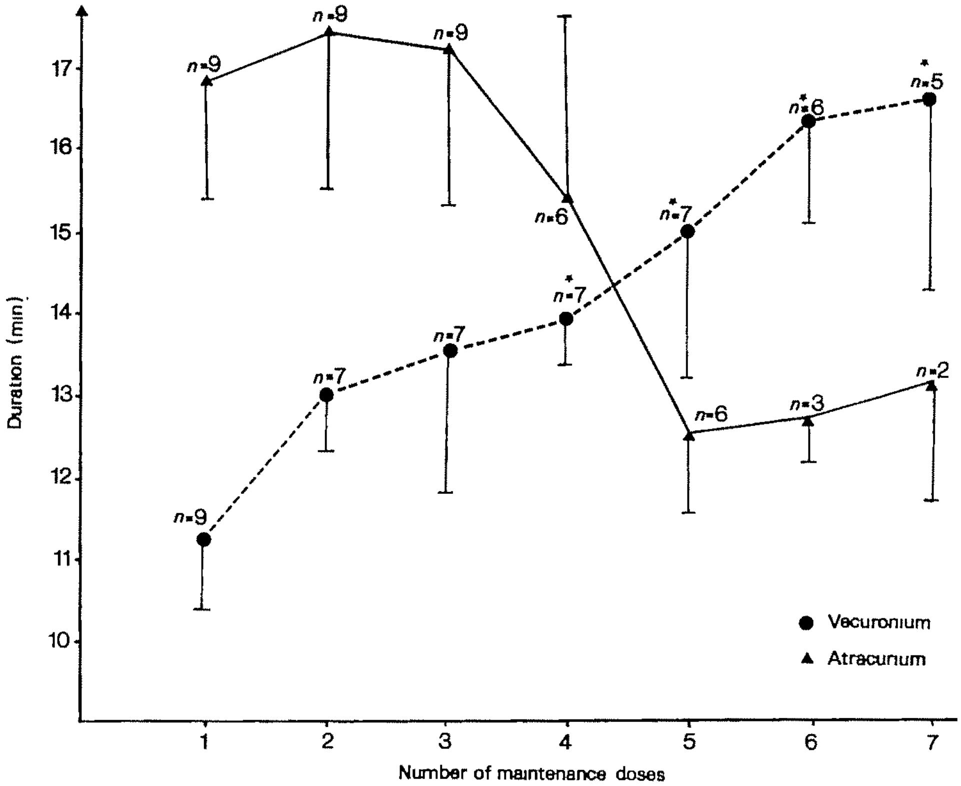

FIG. 2. Mean duration of action of the maintenance doses (mean ± SEM). n = numbers of patients. *$P < 0.05$ *v.* first maintenance dose.

1981; Chapple, Clarke and Hughes, 1983), but flunitrazepam has not been investigated in this respect.

The cumulative-dose technique overestimates the ED_{95} of the intermediate-acting non-depolarizing agents (Fisher et al., 1982; Miller et al., 1984). This has been explained on the basis of the relatively short action of vecuronium and atracurium, particularly in small doses, in relation to the time it takes to administer further increments in a cumulative-dose technique. We used this method because it requires fewer patients than the single bolus method and relatively few patients with no renal function undergo prolonged operations.

The elimination of four patients whose twitch response exceeded the fixed 95% end-point of the cumulative-dose method described by Donlon, Savarese and Ali (1974), might have introduced some bias and produced artificially high values for ED_{50}, ED_{90} and ED_{95}. It is, however, clear that these four patients could not be included in the main part of the study. The aim was to compare the effect of repeated doses of atracurium and vecuronium in patients with end-stage renal failure using maintenance doses calculated from the total initial dose for each patient. Those patients who were eliminated did not lose the twitch response after the initial dose of neuromuscular blocking drug, but after the third incremental dose (three patients) and after the fifth (one). When the dose–response curves were constructed with all the recorded points, the calculated ED_{95} were 204.5 ± 45 µg kg^{-1} for atracurium and 44.1 ± 13.5 µg kg^{-1} for vecuronium. These figures do not differ significantly from the results as presented.

There were two other possible sources of bias in the present study. First, there was no peroperative control of acid–base balance, so that a mild metabolic acidosis cannot be excluded, although all patients had been recently dialysed. This bias could have affected both groups, but in unpredictable ways, since variations in pH have been shown to alter the dynamics of vecuronium in man (Gencarelli et al., 1983), but those of atracurium only experimentally (Hughes and Chapple, 1981).

Second, the release of the vascular clamps on the transplanted kidney was not taken into account in the evaluation of the $Dur_{rep\,25}$. Early excretion of tubocurarine in this situation has been established by Miller and colleagues (1977). The renal excretion of atracurium is assumed to be nil or negligible, but 10–25% of a dose of vecuronium may be excreted in the urine, most of it apparently unchanged (Fahey et al., 1981a; Upton et al., 1982).

In spite of these points, the results of this study were in accord with other published data, and certain aspects may be emphasized. The ED_{50}, ED_{95} and potency ratio of vecuronium and atracurium in patients with end-stage renal failure were comparable to those reported in normal patients when the cumulative-dose technique was used (Gramstad, Lilleaasen and Minsaas, 1983; Robertson et al., 1983). The finding that vecuronium was initially shorter-acting than atracurium—as in normal patients (Hunter, Jones and Utting, 1982, 1984; Foldes et al., 1983; Meistelman et al., 1983; Lebrault et al., 1984)—is in agreement with the work of Bevan and colleagues (1984). Hunter, Jones and Utting (1984) noted a greater variability in response in end-stage renal failure, especially to vecuronium, but this point was not directly investigated in our study.

The lack of cumulation of atracurium has been demonstrated also by kinetic studies in patients with end-stage renal failure (Fahey et al., 1984) and in normal patients (Weatherley, Williams and Neill, 1983) for a geometric progression of doses; its effects depend heavily upon elimination (Miller et al., 1984) as a result of its peculiar spontaneous non-enzymic degradation by the Hoffman route (Stenlake et al., 1981). However, the surprising decrease in the $Dur_{rep\,25}$ observed in this series deserves confirmation and elucidation. Although cumulation of vecuronium could be expected from its kinetic properties (Miller et al., 1984), most dynamic studies in normal patients (Krieg, Crul and Booij, 1980; Fahey et al., 1981b; Buzello and Noldge, 1982; Bevan et al., 1984) and one in patients with end-stage renal failure (Hunter, Jones and Utting, 1984) have failed to find evidence of it. However, two comparative studies with atracurium in normal patients (Ali et al., 1983; Michel et al., 1984) and that of Bevan and colleagues (1984) in patients with end-stage renal failure suggested a tendency to cumulation. Kinetic studies comparing patients with and without renal failure (Fahey et al., 1981a; Bencini et al., 1983; Meistelman et al., 1983) did not find significant clinical differences, but all were based on single, relatively small doses (0.14 mg kg^{-1}, 0.10 mg kg^{-1}, and 0.05 mg kg^{-1} of vecuronium, respectively). The data from the present dynamic trial (interaction time × treatment, increased duration of maintenance doses along with reinjections, cumulation ratio) indicated a cumulation of vecuronium in end-stage renal failure that reached statistical significance after the fourth maintenance dose, although the largest dose administered in the series ($1.8\ \mathrm{mg\ kg^{-1}}$) was relatively small. Whether this cumulation of vecuronium in end-stage renal failure was a result of decreased degradation or elimination, or of redistribution, cannot be elucidated on a dynamic basis. Vecuronium does not seem to be converted in large amounts into active metabolites. Renal excretion by itself does not influence its duration of action, since Fahey and colleagues (1981a) found similar plasma clearances in patients with and without renal failure. An increase in the biliary route in end-stage renal failure has been suggested (Upton et al., 1982; Bencini et al., 1983) and this could become saturated. Nevertheless, in this study the RI of atracurium, which did not cumulate, did not differ from that of vecuronium, which did. This was reported in normal patients by Miller and colleagues (1984) in a review article, but Robertson and colleagues (1983) observed a prolonged RI when three times the ED_{90} was given. Since the RI is assumed to be the best index of the effect of the elimination mechanisms on the overall duration of action of competitive neuromuscular blockers, elimination would not be involved in this dose range in the cumulative effect of vecuronium. Hence saturation of the distribution volume in end-stage renal failure is suggested.

It is concluded that, in patients with end-stage renal failure, vecuronium exhibits a slight, but documented cumulative effect which might make it less safe than atracurium in prolonged surgical procedures . The kinetics and lack of cumulation of atracurium point to the value of an infusion technique in this group of patients.

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Br. J. Anaesth. (1987), 59, 1011–1016

POTENTIATION OF THE NEUROMUSCULAR BLOCKADE PRODUCED BY ALCURONIUM WITH HALOTHANE, ENFLURANE AND ISOFLURANE

S. J. KEENS, J. M. HUNTER, S. L. SNOWDON AND J. E. UTTING

SUMMARY

The potentiation of alcuronium by halothane, enflurane and isoflurane was investigated using electromyography. In the first study, cumulative dose–response curves were constructed in four groups of 10 patients anaesthetized with one of the inhalation agents and nitrous oxide, or with fentanyl and droperidol (control). All three agents reduced the ED_{50} *of alcuronium; the effect was marked with isoflurane* ($P < 0.005$) *but less so with halothane* ($P < 0.05$) *and enflurane (ns). In the second part of the investigation, designed primarily to test the duration of action of alcuronium with each agent, a single bolus dose of alcuronium 0.2 mg kg*$^{-1}$ *was given to four similar groups* ($n = 5$)*. The duration of action was significantly prolonged by enflurane* ($P < 0.01$) *and isoflurane* ($P < 0.05$)*, but not by halothane. The possible reasons for this are discussed.*

Volatile anaesthetic agents are already known to potentiate many competitive neuromuscular blockers. Thus neuromuscular blockade produced by tubocurarine has been shown to be potentiated by halothane (Katz and Gissen, 1967) and, to a greater extent, by enflurane (Lebowitz, Blitt and Walts, 1970) and isoflurane (Miller et al., 1971). Similarly, pancuronium has been shown to be potentiated by halothane (Katz, 1971), enflurane (Schuh, 1983) and isoflurane (Miller et al., 1972). The requirement for alcuronium is also known to be decreased when volatile anaesthetic agents are used (Grimmeisen, 1964), but there is no information available as to the quantitative effect of volatile agents on the block produced by this agent, despite its widespread use in the U.K.

It was decided, therefore, to study the effect of three commonly-used volatile anaesthetic agents, halothane, enflurane and isoflurane, on the neuromuscular blockade produced by alcuronium, monitoring neuromuscular function by electromyography (EMG). Two approaches were used: in the first, conventional cumulative dose–response curves were constructed; in the second, a more clinical approach was used and an attempt was made to determine the effect of the volatile agents on the degree and duration of blockade following a single dose of neuromuscular blocker.

PATIENTS AND METHODS

Ethical committee approval was obtained and a total of 60 patients, scheduled for general surgical or gynaecological operations, gave consent to their inclusion in the study. Each patient was premedicated with promethazine 50 mg orally the night before operation, with or without morphine 10 mg and cyclizine 50 mg i.m. 1 h before the expected start of surgery.

In both parts of the study, the concentrations of the volatile agent(s) were measured using a "Normac" anaesthetic agent monitor (Datex Ltd), the calibration of which had been verified using a flame ionization detector and calibrated gas mixtures. End-tidal carbon dioxide concentrations were measured using a capnometer (Datex Ltd) which had been calibrated against cylinders of known composition. Sampling for both volatile agents and carbon dioxide concentrations was via a cannula inserted through the face mask angle-

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piece and later through the catheter mount. The ECG was monitored continuously and arterial pressure was measured regularly with an oscillotonometer.

Dose–response curves

Four groups each of 10 patients were studied. In the first group (group 1), anaesthesia was induced with fentanyl, droperidol and thiopentone; the patient then breathed nitrous oxide and oxygen (30%) via an anaesthetic face mask, ventilation being assisted if necessary to maintain the end-tidal carbon dioxide concentration between 5 and 6%. At this stage, control EMG traces were obtained.

After this had been achieved, alcuronium was given in divided doses of 50 μg kg^{-1} at intervals of 3 min until the evoked action potential had decreased to less than 10% of control and at least four increments of alcuronium had been given. The study was then terminated, and a tracheal tube was passed.

In the other three groups, induction of anaesthesia was with thiopentone alone. The patient then breathed nitrous oxide in oxygen while control EMG measurements were obtained. Immediately these had been achieved, halothane (group 2), enflurane (group 3) or isoflurane (group 4) was added and, after an induction period of 10 min, end-tidal concentrations were kept constant (to within 0.1%) at 0.75% halothane, 1.7% enflurane and 1.15% isoflurane for a further 10 min, making 20 min in all. Alcuronium was then given in divided doses as described for group 1.

Single bolus dose study

In the second part of the study, 20 patients were given a single bolus dose of alcuronium 0.2 mg kg^{-1}, after control EMG traces had been recorded in the manner described above. Tracheal intubation was performed and anaesthesia supplemented by either fentanyl and droperidol (group 5), halothane (0.4% end-tidal concentration; group 6), enflurane (1% end-tidal concentration; group 7) or isoflurane (0.7% end-tidal concentration; group 8). Artificial ventilation was established and the end-tidal carbon dioxide concentration was maintained throughout anaesthesia between 5–6%, the ventilatory rate being 12–15 b.p.m. Monitoring by electromyography was continued until the first incremental dose of alcuronium was given.

Neuromuscular monitoring

The method of monitoring neuromuscular function by electromyography has been described previously (Calvey, 1984). The skin was cleaned with acetone and the hand immobilized in a splint. ECG electrodes were placed over the ulnar nerve in the forearm for stimulation, and recording electrodes (Conn Med Stress ECG electrodes) placed over the adductor pollicis brevis and the base of the index finger on the palm of the hand. A copper earth electrode was placed between the stimulating and recording electrodes. Stimulation voltage was increased until the evoked compound muscle action potential (CMAP) reached its maximum height, after which the voltage was increased by a further 25% to ensure supramaximal stimulation. The positions of the recording electrodes were adjusted, if necessary, to give a biphasic CMAP trace. The stimulator was set to deliver single pulses with a width of 0.2 ms duration every 12 s (0.0833 Hz) in the first part of the study (groups 1–4) as this mode of stimulation was similar to that used in other work on cumulative dose responses (Donlon, Ali and Savarese, 1974). A train-of-four (2 Hz) every 1 min was used in the second part of the study, as this was more practicable for use over a prolonged period. EMG signals were amplified with an isolated biological amplifier having frequency filters set at 2–3.2 KHz and recorded on u.v. light-sensitive paper from the trace displayed on the oscilloscope of a Medelec MS6 EMG machine.

Method of analysis

In every patient, the height of each action potential was measured and expressed as a percentage of the height of the control. These values were then plotted on a graph against time.

In the first part of the study, the degree of depression of the action potential caused by each increment of neuromuscular blocker was calculated and plotted on log-probit axes (fig. 1). The ED_{50} values were read from these individual dose–response plots. Before comparing these ED_{50} it was necessary to ensure that the lines were parallel. A straightforward mathematical slope could not be determined, since the axes were not linear, one being logarithmic, the other a probit scale. A measure of the slope of each line was, therefore, obtained from a slope function determined by a graphical method (Litchfield and

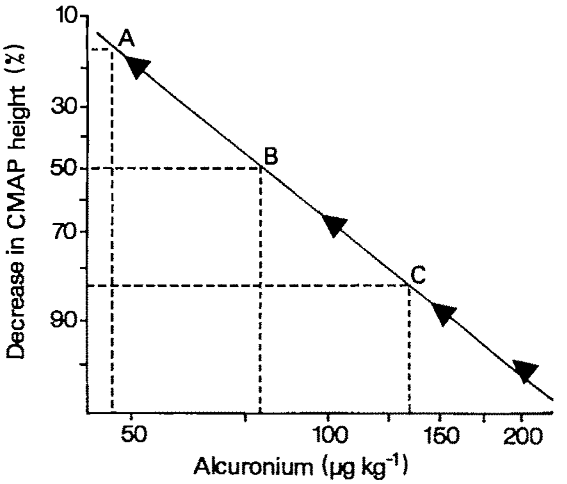

FIG. 1. Log-dose-response curve. Graph drawn from the data obtained from one patient with % decrease in height of compound muscle action potential (CMAP) plotted on a probit scale against the cumulative dose of alcuronium on a logarithmic scale. Point A = ED_{16}; Point B = ED_{50}; Point C = ED_{84}.

Wilcoxon, 1949). The slope function was given by the formula

$$\frac{ED_{84}/ED_{50}+ED_{50}/ED_{16}}{2}$$

The mean slope function of the groups did not differ significantly. The mean ED_{50} values of the groups were then compared using a nonparametric test of significance: the Wilcoxon Rank Sum Test (Wilcoxon, 1945).

In the second part of the study, the rate of recovery from the neuromuscular blockade produced by a standard dose of alcuronium was studied. The time from the maximum depression of the height of the first of the train-of-four action potentials to the point at which the height of the action potential had recovered by one-tenth of that maximum depression was measured in a manner similar to that used by Miller and co-workers (1972). For example, if the height of the control CMAP was 40 mm and this was depressed to 4 mm (90% depression), the time taken to recover by a height of $40-4/10 = 3.6$ mm (i.e. to 7.6 mm) was taken as an indication of the duration of the effect of alcuronium on the CMAP.

RESULTS

Cumulative dose–response curves

The results of the cumulative dose–response study are shown in table I. The apparent ED_{50} of alcuronium with each of the volatile agents was less than it was in the control group. This reduction was greatest with isoflurane ($P < 0.005$). A smaller, although still significant, decrease was found in the halothane group ($P < 0.05$). The mean ED_{50} in the enflurane group (92.6 μg kg⁻¹) was not statistically different from the mean ED_{50} in the fentanyl group (106.8 μg kg⁻¹), even though this difference was greater than that for the halothane group (mean ED_{50} 96.5 μg kg⁻¹). This apparent anomaly is explained by greater variability within the enflurane group.

TABLE I. *The ED_{50} (μg kg⁻¹) for alcuronium is given for each of the four groups studied, together with the SEM. The significance level, obtained using Wilcoxon Rank Sum Test, of a comparison between group 1 and each of the other three groups is also noted. No significant difference (ns) was found between enflurane and fentanyl using this method*

Group	ED_{50}	SEM	Significance level
1. Fentanyl	106.8	5.5	—
2. Halothane	96.5	3.1	< 0.05
3. Enflurane	92.6	3.8	ns
4. Isoflurane	80.5	5.2	< 0.005

Single bolus dose study

The minimum height of the CMAP after a standard 200-μg kg⁻¹ bolus dose of alcuronium was very variable in those patients given an inhalation agent (table II), and ranged from a maximum depression of 2% of control (patient 5 of the enflurane group) to a minimum depression of 22% (patient 4 of the isoflurane group). In contrast, there was much less variation between patients in the fentanyl group (range from 6% to 7% of control).

The time from injection of the neuromuscular blocker to the maximum depression also varied greatly and this variation was especially marked in the enflurane group where it ranged from 8 to 33 min. As can be seen (table II), the variability in the fentanyl group was much less (from 8 to 16 min).

The mean time taken for recovery to one-tenth of the maximum degree of depression was greatest in the isoflurane group (mean 51.6 min) compared with the fentanyl group (mean of 22.6 min); this difference reached a significance level of 0.05.

The increase in mean recovery time in the enflurane group (mean of 40.8 min) was less than that in the isoflurane group but, because of less

TABLE II. *The smallest height of the CMAP as a percentage of control in each of the patients who received a single bolus of alcuronium 0.2 mg* kg^{-1} *is given, together with the mean value obtained in each group. Also recorded is the time from injection of the alcuronium to the maximum depression of the CMAP in each patient and the time to recovery to 1/10 of the maximum depression. Statistical significance using the Wilcoxon Rank Sum Test between the mean value for each group and the mean value for the fentanyl group is also given:* **0.05; **0.01; ns > 0.05*

Group	Patient No.	Minimum height of CMAP (% of control)	Time from injection of relaxant to maximum depression of CMAP (min)	Time to recovery to 1/10 of the maximum depression (min)
5: Fentanyl	1	6.0	8.0	16
	2	7.0	10.0	28
	3	7.0	16.0	16
	4	6.0	15.0	29
	5	7.0	8.0	24
	Mean	6.6	11.4	22.6
6: Halothane	1	14.0	16.0	14
	2	14.0	15.0	19
	3	15.0	8.0	18
	4	4.0	10.0	22
	5	3.0	21.0	41
	Mean	10.0 (ns)	14.0 (ns)	22.8 (ns)
7: Enflurane	1	10.0	9.0	48
	2	8.0	22.0	43
	3	17.0	33.0	31
	4	3.0	10.0	43
	5	2.0	8.0	39
	Mean	8.0 (ns)	16.4 (ns)	40.8**
8: Isoflurane	1	3.0	29.0	62
	2	2.0	10.0	79
	3	7.0	22.0	43
	4	22.0	19.0	25
	5	15.0	19.0	49
	Mean	9.8 (ns)	19.8 (ns)	51.6*

variability within the group, reached a significance level of 0.01.

There was no prolongation of the recovery time in the group of patients anaesthetized with halothane (22.8 min) compared with the fentanyl group (22.6 min).

DISCUSSION

The results of the cumulative dose–response study show a greater effect on the compound muscle action potential by incremental doses of alcuronium when anaesthesia is supplemented by volatile anaesthetic agents. Surprisingly, the smallest effect was in the group anaesthetized with enflurane, which is usually considered to be the most potent agent for potentiating the competitive neuromuscular blockers (Schuh, 1983).

There is a spectrum of potentiation of the competitive neuromuscular blockers, with less potentiation of the shorter-acting drugs such as atracurium (Rupp, McChristian and Miller, 1984) and vecuronium (Rupp, Miller and Gencarelli, 1984) than the longer acting neuromuscular blockers such as pancuronium and tubocurarine. Alcuronium is a synthetic derivative of tubocurarine, which itself is markedly potentiated by enflurane (Schuh, 1983), and it might be expected that alcuronium would be similarly potentiated.

The most obvious possibility for failing to find a marked potentiation by this agent in the dose–response study whilst at the same time finding that the volatile agent markedly prolonged the duration of action of the neuromuscular blocker is that ethical constraints imposed on the investigators meant that time for full equilibration might not have been allowed and, in particular, equilibration at the neuromuscular junction may not have been complete. This factor may well have been more important with enflurane than with the other volatile agents, although it must be said that it is surprising, if this be the case, that the dose–response curves of the enflurane group were closely parallel to the others.

It has been found that potentiation of neuromuscular blockade by enflurane increases linearly with duration of exposure for at least 1–2 h (Stanski et al., 1980). A slow linear increase might not greatly affect the slope of the dose–response curve as the time taken to perform this study was relatively short, but it might be expected that the rate of recovery would be substantially affected by a progressive increase in potentiation of alcuronium if this were measured over a relatively long period of time (the time from injection of neuromuscular blocker until recovery to one-tenth of the maximum depression in the enflurane group was 57.2 min). In fact, there was marked prolongation of the effect of alcuronium by both isoflurane and enflurane, despite only moderate reduction in the ED_{50}. This illustrates a crucial limitation of the value of dose–response curves in determining the potentiation of neuromuscular blockers by volatile agents; with enflurane, at least, different dose–response curves might be obtained for up to 2 h, depending on the duration of exposure to the agent.

There are, however, other problems. The onset time of block by competitive neuromuscular blockers is longer under enflurane anaesthesia than under halothane (Rupp, Miller and Gencarelli, 1984) and, as the increments in the present study were given at regular 3-min intervals, the maximum depression of the CMAP may not have been reached in the enflurane group before the next increment of alcuronium was given—although inspection of the traces suggested that this was not so. The cumulative dose technique is a satisfactory way of comparing different neuromuscular blockers only if their duration of action is long compared with the time taken to perform the cumulative dose–response procedure (Donlon, Ali and Savarese, 1974; Donlon et al., 1980). It is less satisfactory with shorter acting agents of which the duration of action is short relative to the time for the cumulative dose procedure (Ording et al., 1985). In the latter case, erroneous results may be produced because the first dose of the relaxant has worn off appreciably before the last dose has its maximum effect. Alcuronium, however, is sufficiently long-acting to justify the use of the cumulative dose technique. Most studies of potentiation by volatile agents have used mechanical twitch response, although electromyography of the adductor pollicis has been used to show that halothane increased both the degree and duration of neuromuscular blockade caused by atracurium (Stirt et al., 1983). By using electromyography, any direct depressant effect of enflurane on muscular contractility might not be manifest. If the potentiation caused by enflurane was, therefore, largely the result of a direct depressant effect on muscular contraction, studies measuring the effects on muscle cell depolarization (i.e. electromyography) might demonstrate less effect with enflurane.

The fundamental finding of this study is that the action of alcuronium is prolonged markedly both by isoflurane and enflurane. Thus, although the "intubating" dose of alcuronium when using enflurane or isoflurane will be approximately the same as when using a neurolept technique or halothane, the duration of effect of alcuronium will be very much longer in those receiving these agents. Thus problems could arise if incremental doses are given "by the clock" when using these anaesthetic supplements—although the difficulty might be less with halothane or with a neurolept technique. Relative overdose may lead to difficulty in antagonism of blockade at the end of prolonged surgery, as has been shown when enflurane is used in conjunction with pancuronium (Delisle and Bevan, 1982), and it is suggested that some form of monitoring of neuromuscular function should be undertaken when using myoneural blocking drugs in conjunction with enflurane or isoflurane for anything other than short procedures.

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ELECTROMYOGRAPHIC RESPONSES TO SMALL DOSES OF SUXAMETHONIUM IN CHILDREN AFTER BURNS

T. C. K. BROWN AND B. BELL

SUMMARY

Integrated electromyographic studies in burned patients, and in normal controls, during the administration of small doses of suxamethonium (0.1 or 0.2 mg kg^{-1}) have shown that the level of paralysis and the duration of paralysis are significantly increased in burn patients and that the effect is greater with larger burns. Repeated studies on patients using these small doses have shown that patients with burns pass through a phase of extreme sensitivity to the effects of suxamethonium, usually sometime between 4 and 12 days after the burn.

Cardiac arrest has occurred following the administration of suxamethonium to burned patients (Fleming et al., 1960), and recognition of this hazard has led to the avoidance of the use of suxamethonium in such patients. Bush (1964) postulated a number of possible mechanisms and, although it was suspected that hyperkalaemia might be the cause, this was not confirmed until Tolmie, Joyce and Mitchell (1967) reported repeated cardiac arrests associated with acute increases in serum potassium concentation in a badly burned soldier in Vietnam. Keneally and Bush (1974) reported a mean maximum change of 0.13 mmol $litre^{-1}$ after suxamethonium 1.5 mg kg^{-1} in children—the only statistically significant change was in the group aged 5 yr and younger, in which there was a mean maximum increase of 0.23 mmol $litre^{-1}$. Studies reported from our Burn Unit in 1970 showed that the increase in serum potassium concentration appeared to be related to the extent of the burn: an increase of 4.9 mmol $litre^{-1}$ occurred on the 25th day post-burn in a child with 30% burns with only a very transient decrease in cardiac output as assessed by the intensity of heart sounds, while a boy with 10% burns showed an increase in potassium concentration of only 1.7 mmol $litre^{-1}$ (Brown and Bishop, 1970).

Since the hazard of hyperkalaemia appeared to be related to the extent of the burn, and seemed to be greatest between 2 and 6 weeks after the burn, we set out to do a study (using suxamethonium 0.2 mg kg^{-1}) to assess the influences of the extent of the burn, and time following the thermal injury. Unexpectedly, one of the first patients became apnoeic following this dose. Thus we undertook this electromyographic study of responses of normal and burned patients to small doses of suxamethonium.

PATIENTS AND METHODS

Following the induction of anaesthesia with thiopentone two control groups (50 children each) were given suxamethonium, either 0.1 or 0.2 mg kg^{-1} diluted to 1 mg ml^{-1} in sterile water. The selection of burned patients was restricted to those who had an uninjured hand and forearm so that the EMG electrodes could be attached. Thirty-eight burned patients received suxamethonium 0.1 or 0.2 mg kg^{-1} on 59 occasions.

Eleven patients who had repeated anaesthetics were studied on multiple occasions. In these patients the maximum response was used for comparison with the normal controls.

The integrated electromyograph (IEMG) was developed and constructed at the Department of Electrical Engineering at Monash University (Lam, Cass and Ng, 1981). Two stimulating electrodes were placed over the median nerve at the wrist, the recording electrodes over the opponens pollicis muscle and a reference electrode

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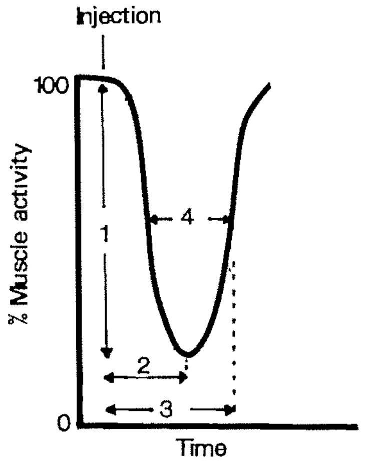

FIG. 1. IEMG pattern showing how the measurements were made from the recording. 1 = Maximum depression in muscle activity (IEMG response). 2 = Time from injection to maximum IEMG depression. 3 = Time to 50% recovery. 4 = Time from 50% of total decrease in activity until recovery to the same level.

was placed on the forearm. A supramaximal stimulus at 1 Hz for 0.1 ms was used to stimulate the median nerve. The depression of the IEMG was recorded on a chart recorder. Measurements were made as illustrated in figure 1.

The non parametric Mann–Whitney *U* test was used for statistical analysis.

RESULTS

Thirty-eight patients were studied on 59 occasions. Suxamethonium 0.1 mg kg^{-1} was given on 19 occasions (11 patients) and there was a statistically significant increase in paralysis (depression of muscle activity) and duration of action compared with controls ($P < 0.001$). There was a similar statistically significant difference between patients with burns receiving suxamethonium 0.2 mg kg^{-1} compared with controls.

The results are summarized in table I and figure 2. The maximum responses were used for patients studied on multiple occasions.

Eleven patients were studied on two or more occasions. Only one of the eight patients given 0.2 mg kg^{-1} had a maximum depression of muscle activity of less than 93%. Two patients given 0.1 mg kg^{-1} had 83% and 93% maximum depression of muscle activity, respectively, while the third, in whom the decrease was 58%, was not studied until 16 days after the burn—which is later than the time of maximum depression seen in the other patients. This occurred between 4 and 12 days (mean 8 days).

Figures 3, 4 and 5 are illustrative of patients studied on multiple occasions. Figure 3 illustrates the depolarization response without any decrease in muscle activity following suxamethonium 0.1 mg kg^{-1} in the early post-burn period. This phenomenon was also seen with this dose in some of the controls. Four days later the patient had a marked response to suxamethonium which lessened on subsequent occasions.

Figure 4 shows the marked responses on all occasions in an older patient with 10% burns receiving suxamethonium 0.2 mg kg^{-1}. Figure 5 shows the marked response to 0.2 mg kg^{-1} on the first occasion, with a reduced response of shorter duration on the second occasion 16 days after the burn.

In general, the greater the degree of paralysis the longer was the duration of effect measured to the time of maximum depression, to 50% recovery and between the midpoints of the downslope and upslope of the IEMG traces (fig. 1).

TABLE I. *IEMG responses to suxamethonium in burns. Statistical significance compared with controls:* *P < *0.01;* **P < *0.005;* ***P < *0.001*

Group	Dose (mg kg^{-1})	*n*	% max. depression in muscle activity	Time to max. depression (min)	Time to 50% recovery (min)	Time 50% dep. to 50% recovery (min)
Control	0.1	50	5.3±1.6	0.22±0.21	0.43±0.15	0.37±0.11
Burns 20+%	0.1	6	54.1±18.7***	0.79±0.18***	1.67±0.90	1.36±0.67
Control	0.2	50	56.6±22.2	0.63±0.19	1.23±0.39	0.99±0.34
Burns < 10%	0.2	10	62.0±32.2	0.97±0.30***	2.19±1.29***	1.85±1.23***
Burns 11–19%	0.2	7	78.4±23.8*	0.94±0.37**	3.05±1.90**	2.72±1.91*
Burns 20+%	0.2	10	76.4±24.2**	1.25±0.46***	3.61±1.70***	3.20±1.59***

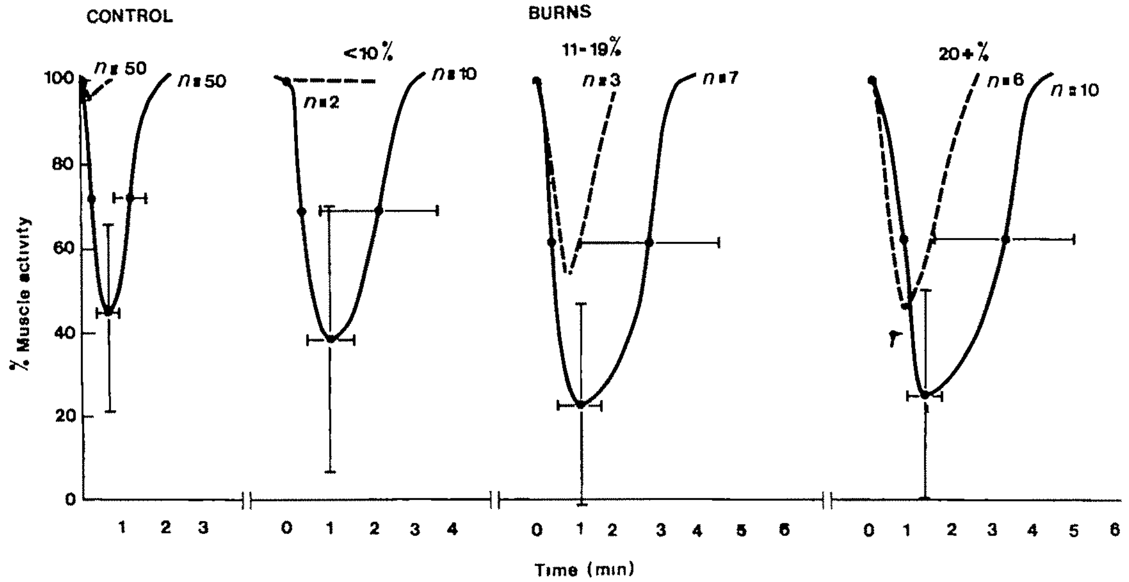

FIG. 2. The mean IEMG recordings for control subjects and patients with burns after suxamethonium 0.1 mg kg^{-1} (dotted lines) and 0.2 mg kg^{-1} (solid lines). SD of maximum depression and time to 50% recovery shown.

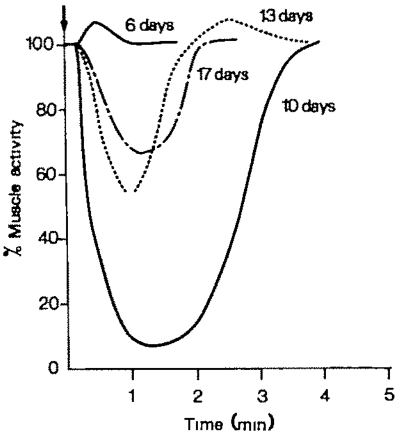

FIG. 3. Degree and duration of paralysis in a 32-kg 6-yr-old (28% of burns) following suxamethonium 0.1 mg kg^{-1}. It demonstrates the increase in sensitivity at 10 days after the burn.

DISCUSSION

Using small doses of suxamethonium, significant differences in response and duration of action were demonstrated in patients with burns compared with normal children. It was found also that patients with burns go through a phase of markedly increased sensitivity to suxamethonium some time between the 4th and 12th days after the burn. At this time the degree of paralysis following 0.2 mg kg^{-1} may cause apnoea and be sufficient to permit intubation of the trachea.

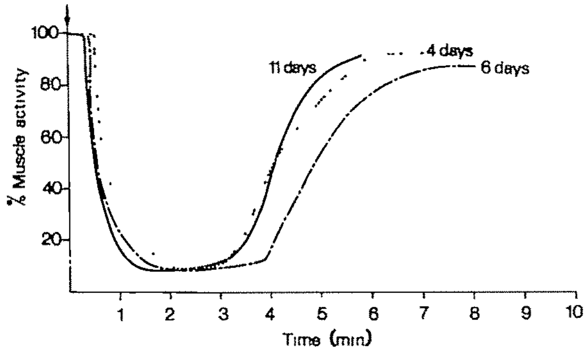

FIG. 4. Marked response in a 55-kg 15-yr-old with only 10% burns on three occasions between 4 and 11 days after the burn—the period when sensitivity to suxamethonium is maximal.

Viby-Mogensen and co-workers (1975a) demonstrated a decrease in plasma cholinesterase activity following thermal injury which correlated significantly with the extent of the burn. The decrease to minimum values occurred most rapidly in patients with a burn index greater than 30%. Most of this decrease occurred during the first 2 days after the injury. The duration of the depression in cholinesterase activity was some-

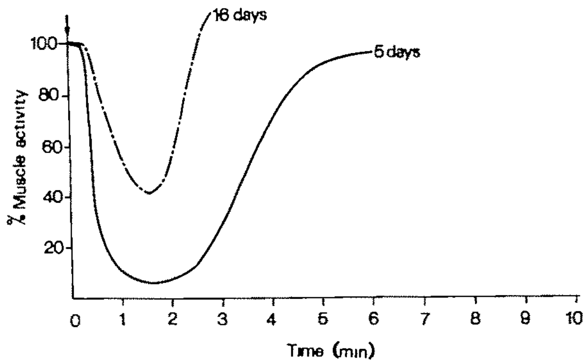

FIG. 5. A child with 20% burns showing a marked difference in response between 5 and 16 days after the burn following suxamethonium 0.2 mg kg^{-1}.

times prolonged and in some patients normal values were not regained for some weeks after full recovery.

Although the decrease in plasma cholinesterase concentration could result in an exaggerated response to suxamethonium, the fact that the maximum depression of IEMG activity occurs later suggests that it is not the only factor increasing the sensitivity to suxamethonium in burned patients.

Viby-Mogensen and co-workers (1975b) demonstrated a significant correlation between the maximum increase in serum potassium concentration and the extent of the burn when suxamethonium was given after the 14th day. They also noted that major increases before that time occurred only with very extensive burns. Our experience suggests that the greatest increases in serum potassium concentration occur during the 3rd and 4th weeks after the burn (Brown and Bishop, 1970). This is later than the time at which the maximum responses occurred in this study. In two of our patients who showed a markedly greater depression of muscle activity, blood samples taken each minute from 0 to 5 min after suxamethonium, showed no change in serum potassium concentration. In another child, with 30% surface area burns whose potassium concentrations were measured on nine occasions after suxamethonium 0.1 mg kg^{-1}, plasma potassium concentration decreased until 15 days after the burn, when an increase of 0.3 mmol $litre^{-1}$ occurred. The maximum increase in plasma potassium concentration (0.4 mmol $litre^{-1}$) occurred on the 26th day after the burn. The maximum depression of muscle activity (IEMG) occurred on day 12. It appears that the exaggerated neuromuscular blocking effects are not related to the hyperkalaemic response to suxamethonium.

We have shown that, after burns, children exhibit an increased degree and duration of paralysis following small doses of suxamethonium. They pass through a phase of exquisite sensitivity which occurs sometime between the 4th and 12th days after the burn, when they will become paralysed (and the trachea can be intubated) with doses as small as 0.2 mg kg^{-1}. Although intubation can be performed with much reduced doses of suxamethonium—which will not cause dangerous increases in serum potassium concentration—it is not usually necessary to use this neuromuscular blocking drug, and it is generally advisable not to use suxamethonium in patients with large burns. Non-depolarizing drugs can be used, but larger doses than normal, particularly of tubocurarine, may be required (Brown and Fisk, 1979; Martyn et al., 1980).

The maximum changes in plasma cholinesterase activity, sensitivity to suxamethonium and potassium concentration after suxamethonium do not occur at the same times after the burn. Although the first two changes may have some interrelation, neither is related to the increase in the release of potassium.

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EFFECT OF HALOTHANE, ENFLURANE AND ISOFLURANE ON BRONCHOMOTOR TONE IN ANAESTHETIZED PONIES

G. C. G. WATNEY, C. JORDAN AND L. W. HALL

SUMMARY

The effects of halothane, enflurane and isoflurane on bronchial calibre were investigated in five anaesthetized ponies using a computer-aided forced airflow oscillation technique to derive specific lower airways conductance ($s.G_{law}$) *and expiratory reserve volume (ERV). All the agents tended to increase* $s.G_{law}$ *(indicating bronchodilatation), but ERV was reduced by halothane and enflurane, and increased by isoflurane. It was concluded that the effects of these agents on bronchomotor tone were similar to those which occur in man. However, the reasons for the differences in their effects on ERV compared with those found in man remain to be determined.*

In general, halothane and enflurane cause bronchodilatation and a reduction in airway resistance in man and small animals (Aviado, 1975; Lehane, Jordan and Jones, 1980), and Heneghan and colleagues (1986) have reported that isoflurane may also produce bronchodilatation in man—although this is less marked than following halothane. It has been suggested that the anatomical and physiological similarities of equine and human lungs may make the horse a more useful experimental model for man than, for example, the dog (McLaughlin, Tyler and Canada, 1961). However, there appears to be no previous information on the responses of the equine airway to inhalation anaesthetics, primarily because of the difficulties of measuring airway resistance in anaesthetized large animals while making allowances for any changes in lung volume. These changes are known to be induced by inhalation anaesthetic agents in man (Lehane, Jordan and Jones, 1980; Heneghan et al., 1986) and affect airway resistance as a result of the hyperbolic relationship between airway resistance and lung volume.

This paper describes the effects of halothane, enflurane and isoflurane on bronchial calibre of ponies, measured by a technique which enables the separation of changes in bronchomotor tone from changes in lung volume (Jordan et al., 1981).

MATERIALS AND METHODS

Animals

Five adult Welsh ponies (three females and two geldings), free from clinically detectable signs of cardiopulmomary disease, ranging in age from 3 to 16 yr and in weight from 199 to 331 kg, were used in these investigations. The animals were kept at grass except for an 18-h fast before each study, when they were stabled and bedded on wood shavings. During this period they were allowed unrestricted access to drinking water. The animals were exposed to each agent once, and were anaesthetized on separate occasions for exposure to the three inhalation agents studied.

Measurements

Specific lower airways conductance ($s.G_{law}$) and expiratory reserve volume (ERV) (which in this context refers to the volume of air extracted from the lungs between functional residual capacity (FRC) and the point at which airway resistance tends to infinity) were measured during general anaesthesia using a modification of the computer-assisted forced oscillation technique described for use in patients by Jordan and co-workers (1981). A sinusoidally oscillating airflow (peak flow 2.2 litre s^{-1}) was produced by a 350-ml stroke volume piston pump operating at 2 Hz. Airflow was measured at the airway opening by a screen pneumotachograph (F1000L, Mercury Electronics) and airway pressure measured at the

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tip of the tracheal tube using matched differential pressure transducers (Validyne MP45). Ventilatory resistance was calculated from the pressure and flow signals by a purpose-built analogue computer and changes in lung volume (from FRC) were calculated by integration of the flow signal. Analogue output signals from the computer proportional to ventilatory resistance and lung volume were fed into a microcomputer (Apple //e, Apple Computer Inc.). via an analogue to digital converter (AI13 Analogue Input System, Interactive Structures Inc.). Initial estimates of s.G_{law} and ERV were calculated from the hyperbolic resistance–lung volume data using a statistical curve-fitting routine (Jordan et al., 1981). Using these values as starting points, final estimates were derived by the iterative method of Hey and Hey (1960).

Procedure

Anaesthesia was induced by a solution of 10% chloral hydrate in 5% dextrose, infused i.v. until the animal became ataxic, followed by a rapidly injected bolus of thiopentone sodium 10 mg kg^{-1}. This regimen was chosen because it provides 20–30 min of surgical anaesthesia, and so should eliminate the possibility of awareness during a period of neuromuscular blockade. With the animal positioned in left lateral recumbency, a 20-mm cuffed tracheal tube was inserted and connected to a large animal circle system. After it had been determined that the animal was unconscious, paralysis of the ventilatory muscles was produced by an i.v. injection of pancuronium bromide 0.1 mg kg^{-1}. Intermittent positive pressure ventilation with oxygen was provided by a ventilator suitable for large animals (Cambridge Ventilator, Bowring Engineering) and adjusted to maintain the end-tidal carbon dioxide concentration (continuously measured with a mass spectrometer) between 5 and 6%. During the period of paralysis, the animals were monitored for signs of awareness, such as tachycardia, spontaneous movements or lachrymation and, if these were observed, increments of thiopentone 3 mg kg^{-1} were administered.

When measurements were required, the ventilator was switched off at peak inspiration, and resistance continuously measured while the lungs were deflated at a rate of 300 ml s^{-1} via a vacuum pump. Measurement was terminated when the resistance reached 0.2 kPa $litre^{-1}$ s or airway pressure reached 4 kPa less than atmospheric.

In each investigation, four control measurements were obtained from the animal during the period of chloral hydrate–thiopentone anaesthesia. The required inhalation anaesthetic was then introduced to the circuit at a concentration approximately equal to double the MAC (2% halothane, 3% isoflurane and 4% enflurane), delivered from a vaporizer (Fluotec, Enfluratec and Isotec; Ohmeda) in oxygen at a rate of 8–10 litre min^{-1}. The MAC values of these agents in equines are 0.88% for halothane, 2.12% for enflurane and 1.31% for isoflurane (Steffey et al., 1977). The end-tidal anaesthetic concentration was continuously monitored (Engstrom Emma) and measurements made at 5-min intervals for 30 min. At the end of each study, the administration of the anaesthetic was discontinued, neuromuscular blockade antagonized with neostigmine 7.5 mg (plus atropine 18 mg), and the animal allowed to recover.

Statistics

Since values of s.G_{law} were found to have a skewed distribution, and since the changes were dependent upon their initial values, logarithmic transformation was carried out on the data before analysis.

In order to determine the reproducibility of the technique and the significance of day-to-day changes in the indices obtained during the control period of chloral hydrate–thiopentone anaesthesia, the four control measurements from each animal (obtained on each of the three occasions it was anaesthetized) were compared using one-way analysis of variance. The significance of the effects of the agents in each individual animal was assessed by comparing the four control values obtained during chloral hydrate–thiopentone anaesthesia with the six values obtained during the administration of each agent using a two-sample *t* test. Overall the significance of group changes produced by each agent at each time during exposure was determined using the average of the four control readings and two-way analysis of variance followed, where appropriate, by paired *t* tests.

RESULTS

Control values, reproducibility and day-to-day variation

The means of the average of the four control values of the various indices obtained from the five animals did not differ significantly before exposure to each inhalation agent (table I). The

TABLE I. *Mean (SEM) of the average control values of ln s.G_{law} (original units kPa^{-1} s^{-1}) and ERV obtained from each animal during chloral hydrate–thiopentone anaesthesia before exposure to the three inhalation anaesthetics*

	Halothane	Enflurane	Isoflurane
ln s.G_{law}	1.79 (0.15)	1.59 (0.10)	1.80 (0.23)
ERV (litre)	3.61 (0.69)	4.71 (0.64)	4.33 (1.02)

TABLE II. *A = Mean standard deviation of the control values of the variables studied obtained during chloral hydrate–thiopentone anaesthesia in the 15 experiments. B = Mean standard deviation of the average of the four control values obtained from each animal on the three occasions it was anaesthetized. C = Number of animals showing significant (P < 0.05) variation in the control values when they were anaesthetized on different occasions for exposure to each agent*

	A	B	C
ln s.G_{law}	0.16	0.65	4
ERV (litre)	0.26	2.13	5

results obtained during any one control period of chloral hydrate–thiopentone anaesthesia were reproducible, but large variations in the control values were found when the animals were anaesthetized on different occasions for exposure to the three anaesthetic agents (table II).

Exposure to inhalation anaesthetics

No significant differences were found in the end-tidal concentration of each agent when expressed as a fraction of its MAC value (fig. 1).

Exposure to halothane (fig. 2) resulted in a moderate degree of bronchodilatation (indicated by an increase in s.G_{law}) and decrease in ERV. Whilst the overall changes in s.G_{law} and ERV were not statistically significant (analysis of variance), a significant degree of bronchodilatation was found in two of the animals (table III, two sample t test) and none showed significant bronchoconstriction. Two animals showed a significant reduction in ERV.

Enflurance produced more consistent changes than halothane. Significant bronchodilatation was observed at all times after exposure (fig. 3), the individual response being significant in four of the five animals (table III). A reduction in ERV was observed which reached significance after 30 min (fig. 3).

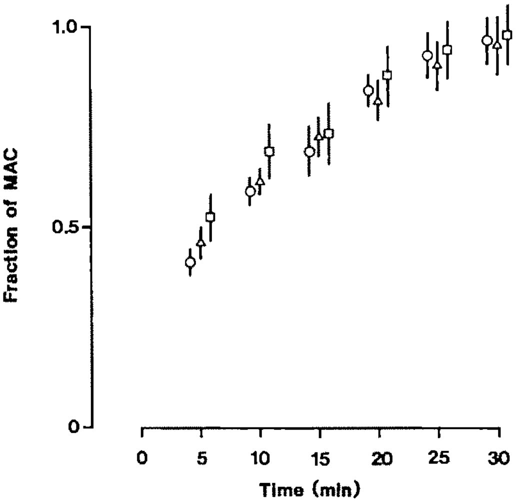

FIG. 1. Mean (SEM) end-tidal concentrations of halothane (○), enflurane (△) and isoflurane (□) expressed as fraction of MAC at each time of measurement.

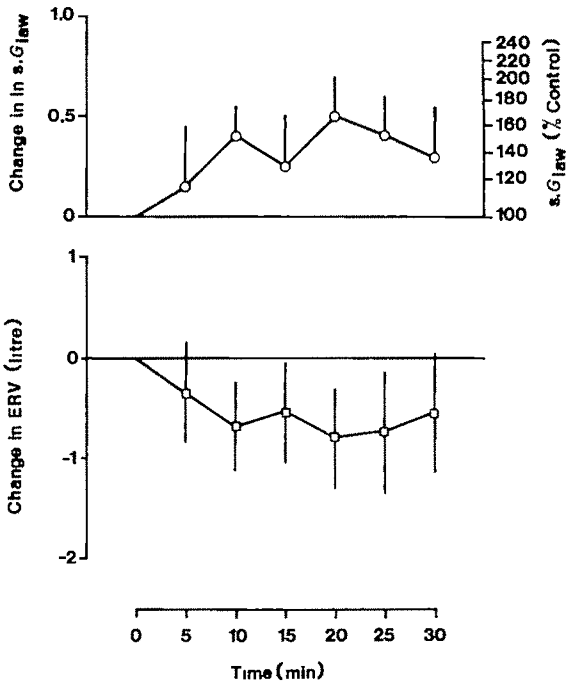

FIG. 2. Mean (SEM) values of changes in ln s.G_{law} and ERV during exposure to halothane.

The bronchodilatation produced by isoflurane was similar to that observed with halothane, except that it appeared to occur more rapidly, the maximum degree of bronchodilatation being evident within 5 min of exposure (fig. 4). The proportion of animals showing significant changes

TABLE III. *Number of animals showing significant ($P < 0.05$, two-sample* t *test) changes after exposure to inhalation agents. Inc. = Significant increase; Dec. = significant decrease; NC = no significant change*

	Halothane			Enflurane			Isoflurane		
	Inc.	Dec.	NC	Inc.	Dec.	NC	Inc.	Dec.	NC
ln $s.G_{law}$	2	0	3	4	0	1	2	0	3
ERV (litre)	0	2	3	0	2	3	2	0	3

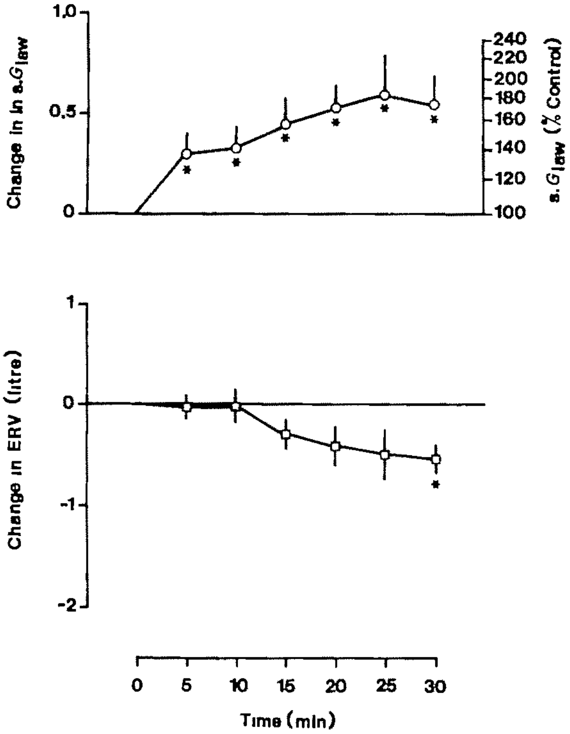

FIG. 3. Mean (SEM) values of changes in ln $s.G_{law}$ and ERV during exposure to enflurane. $^*P < 0.05$.

was similar to that with halothane (table III). In contrast, with halothane and enflurane, no change in ERV was evident for about 15 min, after which it progressively increased, being significantly greater ($P < 0.05$, paired *t* test) than control after 30 min.

Bronchodilatation was produced by all three agents in only one pony, and in one by enflurane and isoflurane but not halothane. No consistent pattern was observed in the changes in ERV in the individual animals after the different agents.

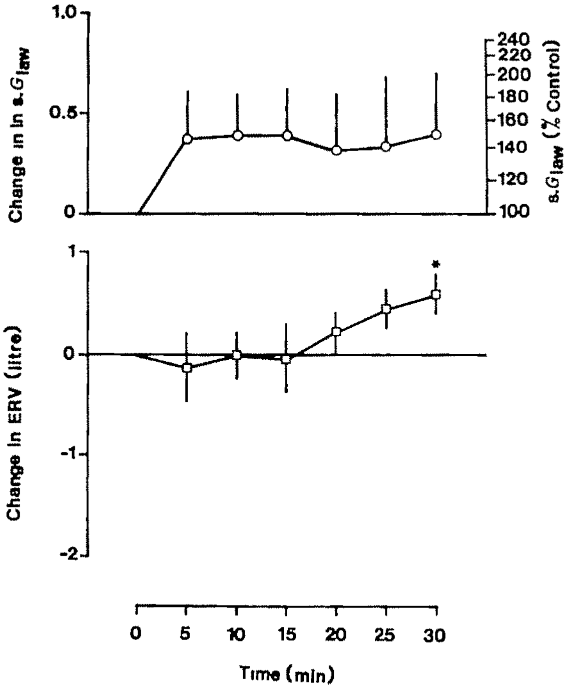

FIG. 4. Mean (SEM) values of changes in ln $s.G_{law}$ and ERV during exposure to isoflurane. $^*P < 0.05$.

DISCUSSION

All the agents used in this study tended to produce bronchodilatation, which is in accord with previous observations in man and other animals (Aviado, 1975; Lehane, Jordan and Jones, 1980; Heneghan et al., 1986), although the overall changes were only statistically significant during exposure to enflurane. The increase in $s.G_{law}$ with halothane was broadly comparable in magnitude to that previously found in man and it may be that the failure to demonstrate significant bronchodilatation was a reflection of the small sample size. In contrast with the results of Heneghan and colleagues (1986), isoflurane appeared to produce a similar degree of bronchodilatation to halothane. However, as these authors suggested, this may have been attributable to the significantly higher control values of $s.G_{law}$ in the group of their patients which received isoflurane. The results of this study show that enflurane produces bronchodilatation in ponies, as in man, and suggest that the effects of halothane and isoflurane are probably similar in equine and human patients.

The changes in ERV are of particular interest since ERV has been found to increase under halothane and isoflurane in man (Heneghan et al.,

1986) and with halothane in cattle (Watney, 1985). Why the effects should be different in ponies, and vary with the different agents, is not clear. There would appear to be three possible means by which inhalation anaesthetic agents may induce acute changes in ERV. First, changes in the lung elastic recoil forces may affect the structural support provided to the lower airways and thus influence the volume at which collapse occurs. Such changes might be produced by surface effects (Wilson, 1981), variations in the intrapulmonary blood volume (Gianelli, Ayres and Buehler, 1967) or the activity of smooth muscle within the lung, including that of the lower airways themselves (Smith, Butler and Hoppin, 1984). Second, systemic vasodilatation might lead to a redistribution of blood out of the thoracic cavity and an increase in intrathoracic gas volume (Hedenstierna, Johansson and Linde, 1982). Third, changes in the abdominal blood volume may lead to displacement of the diaphragm (Jones et al., 1979). If this is of importance, the relatively large abdominal content of horses and the positioning of the animals in lateral recumbency may lead to differences in the displacement of the diaphragm compared with that found in supine human patients. However, at present any such hypothesis is speculative and it is evident that further work is required to establish the mechanisms by which inhalation anaesthetic agents may acutely affect ERV.

ACKNOWLEDGEMENTS

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SELECTIVE MECHANICAL VENTILATION OF DEPENDENT LUNG REGIONS IN THE ANAESTHETIZED HORSE IN DORSAL RECUMBENCY

G. NYMAN, C. FROSTELL, G. HEDENSTIERNA, B. FUNKQUIST, C. KVART AND H. BLOMQVIST

SUMMARY

The effects of selective mechanical ventilation of dependent lung regions were studied in anaesthetized horses (mean weight 486 kg) in dorsal recumbency. Blood-gas measurements were performed with the horse in the lateral position during spontaneous breathing (before selective intubation) and in dorsal recumbency during spontaneous breathing, general mechanical ventilation, and spontaneous breathing+selective mechanical ventilation. Arterial oxygen tension (Pa_{O_2}) was 32.3 kPa in the lateral position during spontaneous breathing with a high inspired oxygen fraction ($FI_{O_2} > 92\%$). In dorsal recumbency Pa_{O_2} decreased to 10.9 kPa during spontaneous breathing and was not significantly affected by general mechanical ventilation (Pa_{O_2} 12.6 kPa). The institution of selective mechanical ventilation with a selective positive end-expiratory pressure (PEEP) of 20 cm H_2O caused a marked increase in Pa_{O_2} to an average of 35.3 kPa. It is concluded that selective intubation of dependent regions in the diaphragmatic lobes is a feasible procedure and that selective mechanical ventilation with PEEP markedly improves arterial oxygenation in the anaesthetized horse in dorsal recumbency.

It has been known for more than 20 years that the alveolar–arterial oxygen tension difference is markedly increased in the anaesthetized recumbent horse (Hall and Clarke, 1983; Taylor, 1984). In a study on anaesthetized horses, the position of dorsal recumbency was shown to impede pulmonary gas exchange even more than the lateral position, the arterial oxygen tension (Pa_{O_2}) during spontaneous breathing of 90–100 % oxygen decreasing to a value of 8–10 kPa (Nyman, Funkquist and Kvart, in preparation). However, recumbency appears to explain only partially the impairment in gas exchange (Hall, 1984) and the anaesthetic itself must be held largely responsible for this change. In this paper we present a new technique of ventilating the anaesthetized, recumbent horse, based on selective ventilation, and the application of positive end-expiratory pressure (PEEP) to dependent lung regions. The rationale of using this technique, the procedure, and preliminary results concerning arterial blood-gas tensions are described.

THEORY

In the lateral position, the volume of the dependent lung in the anaesthetized horse is markedly reduced (McDonell, 1974) and the ventilation of that lung is impeded and becomes only one-fifth of the total ventilation (McDonell, 1974). The perfusion of the dependent lung may also be reduced (Staddon and Weaver, 1981; Stolk, 1982), but to a lesser extent than the ventilation (Hall and Clarke, 1983), thus creating a ventilation–perfusion mismatch. In radiographic studies opacities have been seen to develop in the lower lung of anaesthetized laterally recumbent horses (McDonell, Hall and Jeffcott, 1979). Histological examination of rapidly frozen lung

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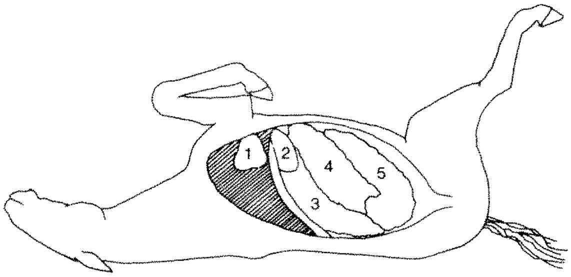
tissue has shown a well expanded upper lung, and atelectasis and large alveolar capillaries in the lower lung (Stolk, 1982). These findings may indicate airway or alveolar collapse, or both, and vascular congestion during anaesthesia in the recumbent horse. In addition, the weight of abdominal organs on the slanting diaphragm in the horse in dorsal recumbency may cause compression of the lower lobe of both lungs (fig. 1).



Dorsal Recumbency

FIG. 1. The horse in dorsal recumbency, illustrating the relation between the lungs, diaphragm and abdominal organs. Note how the slanting diaphragm allows the abdominal contents to encroach on the diaphragmatic lobes of the lung. Redrawn on basis of x-ray studies by McDonell, Hall and Jeffcott (1979). 1 = Heart; 2 = stomach; 3 = dorsal colon; 4 = ventral colon; 5 = caecum.

The application of general PEEP would be expected to improve pulmonary gas exchange by increasing the lung volume and opening up airways and alveoli. However, general PEEP has been shown to have no beneficial effect on the arterial oxygenation in the anaesthetized spontaneously breathing horse (Beadle, Robinson and Sorenson, 1975; Hall and Trim, 1975). This led Sorenson and Robinson (1980) to conclude that PEEP does not increase the lung volume enough to counter airway closure and alveolar collapse, and that these events are not important in limiting gas exchange.

We hypothesize that alveolar collapse and airway closure in dependent lung regions *are* important contributors to hypoxaemia in the recumbent, anaesthetized horse. We consider this hypothesis to be supported by the severely congested and apparently collapsed lung tissue in the diaphragmatic regions that we have observed in horse lungs excised shortly after death under general anaesthesia in a position of dorsal recumbency (fig. 2). Therefore, we assume that generally applied PEEP of up to 20 cm H_2O (as has been used in previous studies) is not enough to open up closed regions. On the other hand, a further increase in overall PEEP may be detrimental, since it has been demonstrated that the

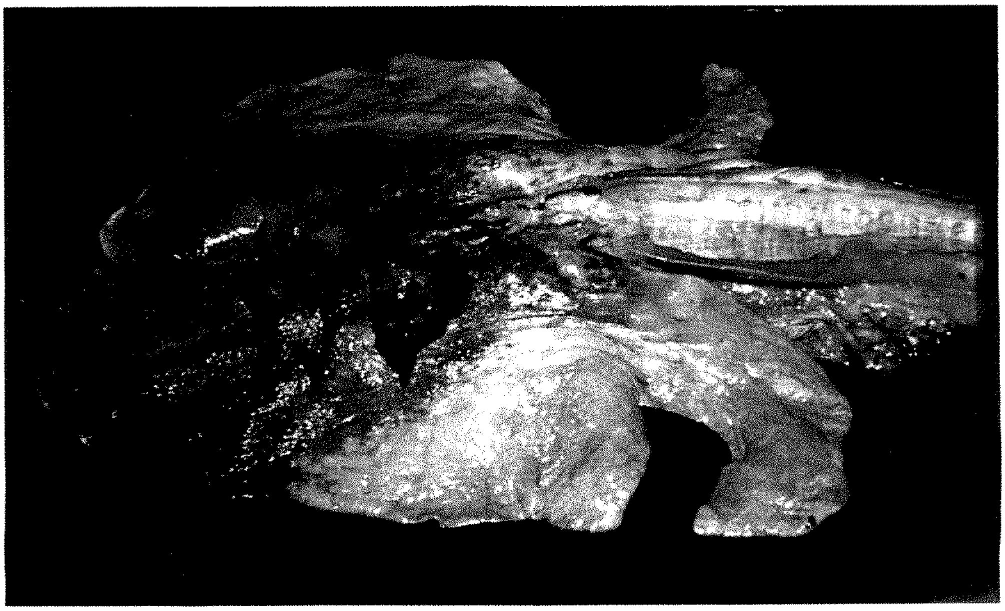


FIG. 2. Photograph of freshly excised lungs from a horse which died under anaesthesia in a position of dorsal recumbency. The dorsal aspect is shown, with the trachea to the right and caudal regions of the diaphragm to the left. Note the severely congested diaphragmatic regions. The cuts through the lung were made to show the congestion in the tissue.

increases in regional volume caused by PEEP are distributed unfavourably and cause mainly a further expansion of already well-expanded lung regions (Hedenstierna et al., 1981). This increases the danger of barotrauma (Kumar et al., 1973) and forces lung blood flow to dependent lung regions, that are poorly ventilated or not ventilated at all, enhancing ventilation–perfusion ($\dot{V}/\dot{Q}$) inequality (West, Dollery and Naimark, 1964). In man PEEP also reduces the cardiac output, presumably by impeding the venous return to the thorax (Colgan and Marocco, 1972). This will further aggravate the hypoxaemia caused by a $\dot{V}/\dot{Q}$ mismatch, since the mixed venous blood will be more desaturated at low cardiac output (for a given oxygen consumption).

Ideally, ventilation should be distributed in proportion to regional blood flow and with least possible interference to the blood flow. In man this can be accomplished by placing the subject in the lateral position and ventilating each lung separately by means of a double-lumen bronchial tube. In this way the ventilation of the dependent lung can be increased to match its perfusion (independent or differential ventilation) and, by applying PEEP solely to that lung, closed and collapsed regions can be opened up to improve the distribution of ventilation within the lung (selective PEEP) without any overdistension of non-dependent lung regions. This technique has proved successful both in healthy subjects during anaesthesia and in patients in the intensive care environment (Baehrendtz and Hedenstierna, 1984; Hedenstierna et al., 1984).

We have adopted the basic principles of this concept for a technique suited to the horse. Since the impairment of gas exchange appears to be much more marked in a position of dorsal recumbency than in the lateral position, we have focused our interest on developing or modifying the technique for that position.

MATERIALS AND METHODS

Technique for selective ventilation and PEEP

A technique for the selective administration of ventilation and PEEP was developed and tested in adult standard-bred trotter horses anaesthetized as described below. The animal ethics committee approved the study.

Material and anaesthesia. Five horses were investigated: two geldings and three mares weighing between 405 and 532 kg. Four of these were studied during generally applied and selective mechanical ventilation (Nos. 1, 2, 4, 5 in table I). Individual data are given in table I. The horses were considered healthy at clinical examination, including inspection of the airways with a fibreoptic bronchoscope (CF-LB 3, Olympus). The horses did not receive any food for 12 h before anaesthesia, but had free access to water and straw bedding. They were premedicated with acepromazine 0.05 mg kg^{-1} i.m. 1 h before induction of anaesthesia. A centrally acting muscle relaxant, 5 % glyceryl guaiacolate was given by i.v. infusion until the horse became unstable and could be pulled down onto a mattress by means of ropes around the neck and chest. Anaesthesia was then induced with 12.5% thiopentone i.v. (0.4 g/100 kg) and the trachea intubated with a cuffed tracheal tube (Rüsch, i.d. 20 mm). Anaesthesia was maintained with halothane in oxygen in a large animal circle type rebreathing system with a carbon dioxide absorber and a halothane vaporizer (Fluotec Mark 3). The fresh gas flow (oxygen) was 5 litre min^{-1}. The halothane concentration was adjusted to maintain the level of anaesthesia at stage III, plane 1–2 (Guedel, 1937; Campbell and Lawson, 1958). During part of the study the horse was mechanically ventilated using a large animal ventilator based on the bag-in-box principle (Smith, 1971). The ventilator was set to deliver a tidal volume of oxygen 7–9 litre at a rate of 6 b.p.m. The maximum inspiratory pressure during general mechanical ventilation was 30 cm H_2O.

TABLE I. *Details of horses studied*

No.	Breed	Sex	Age (yr)	Weight (kg)
1	Standard-bred trotter	Gelding	11	530
2	Standard-bred trotter	Mare	15	525
3	Standard-bred trotter	Mare	4	562
4	Standard-bred trotter	Gelding	7	440
5	Standard-bred trotter	Mare	3	405
Mean			8.0	492
SEM			±2.2	±30

Technique. (Anatomical nomenclature according to Hare (1975).) A tracheotomy was performed in the middle of the neck, just beyond the tip of the tracheal tube. Two tracheal tubes for human use (Portex No. 9 with inflatable high volume cuffs), connected to 1.0-m long catheters, were guided through the tracheostomy to a dependent region of each diaphragmatic lobe, using a fibreoptic bronchoscope (Olympus CF-LB 3). The tracheal wound was temporarily made airtight around the tubes by means of Ardent Alginate (Class B Type II, Dental Medico).

The two catheters were connected to a clinical ventilator (UV 705, AGA) by a Y-piece. The expiratory port of the ventilator was connected to tubing which ended in a water trap which was adjusted to create a PEEP of 20 cm H_2O. The maintenance of a stable value of PEEP was considered proof of an airtight seal between the catheters and the bronchi. The tidal volume was set at oxygen 1.5 litre at a rate of 10 b.p.m. and the maximum inspiratory pressure was approximately 40 cm H_2O. The horse was breathing spontaneously through the regular tracheal tube, ventilating the remaining, major part of the lung tissue, simultaneously with the mechanical ventilation of the dependent lung regions (fig. 3). However, there was no synchronization between the spontaneous breathing and the ventilator. Inspiratory gas samples were drawn intermittently from the large animal circle during spontaneous breathing and general mechanical ventilation, and from the open circuit (UV 705, AGA) during selective ventilation. Subsequent mass spectrometer analysis showed that the inspired oxygen fractions always exceeded 92%.

Positioning of the bronchial catheters. In all horses the positioning of the catheters was accomplished smoothly and no difficulties were encountered in reaching the dependent regions of the lower lobes. In choosing appropriate sites for the bronchial catheters, our own observations in a dissected animal which had died in a position of dorsal recumbency were taken into consideration (fig. 2). The tips of the tubes were advanced approximately 10 cm past the tracheal bifurcation into the diaphragmatic lobar bronchus. The cuffs of the tubes were inflated immediately before the branching off the lateral basal segmental bronchus. This allowed selective mechanical ventilation of the lateral basal and dorsal basal segments of the lower lobes (fig. 4).

Gas exchange study

Gas exchange was studied by means of arterial blood-gas measurements in the five horses while standing and during anaesthesia as described above.

Blood-gas tensions. Arterial blood samples were taken by puncture of the carotid artery in standing horses and through a catheter placed in the metatarsal artery during recumbency. Pa_{O_2}, carbon dioxide tension (Pa_{CO_2}) and pH were measured, standard techniques being used (ABL3 Radiometer, Copenhagen, Denmark). The blood-gas data were corrected to the body temperature of the horse.

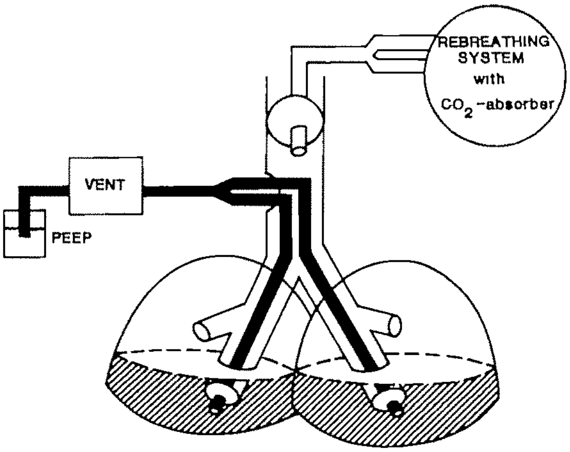


FIG. 3. Schematic drawing illustrating selective intubation of the dependent regions of the diaphragmatic lobes. The tips of the tubes were advanced to a position approximately 10 cm distal to the carina and lay just above the branching of the diaphragmatic lower bronchus into the lateral basal and the basal segmental bronchi. Vent. = ventilator.

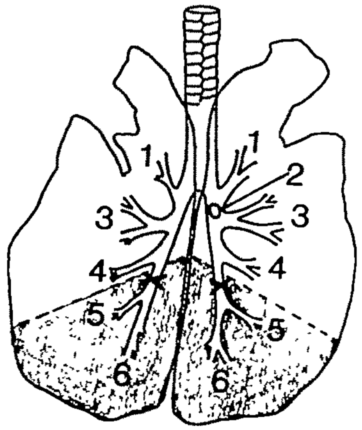


FIG. 4. Bronchial anatomy of the horse, and the positioning of the endobronchial catheters in the diaphragmatic lobar bronchus. (Redrawn from Hare (1975).) 1 = Apical lobar bronchus; 2 = accessory lobar bronchus; 3 = middle segmental bronchus; 4 = ventral basal segmental bronchus; 5 = lateral basal segmental bronchus; 6 = dorsal basal segmental bronchus. Nos 3–6 are branches of the diaphragmatic lobar bronchus.

Procedure. After blood sampling in the standing, unsedated horse, anaesthesia was induced. The trachea was intubated and connected to the anaesthetic breathing system. Further blood samples were drawn while the horse was in the lateral recumbent position, breathing spontaneously for 30–60 min. The horse was then turned to a position of dorsal recumbency, its posture being supported by wings on a specially designed surgical table. After another 30–60 min of spontaneous breathing, blood was again collected and blood-gas analysis undertaken, and general mechanical ventilation was instituted with a moderate hyperventilation with a tidal volume adjusted to keep the Pa_{CO_2} at 5–6 kPa. This was followed by further blood sampling after a similar period of time. To initiate spontaneous breathing, the frequency of ventilation was reduced in order to increase Pa_{CO_2}. After the return of spontaneous breathing, tracheotomy was performed and the catheters were introduced, one to each dependent region of the diaphragmatic lobe. While the horse was breathing spontaneously, selective mechanical ventilation of and PEEP to the lower lung regions was commenced and after 30–60 min blood samples were drawn. In three horses blood-gas measurements were performed in dorsal recumbency after 15–30 min of selective ventilation of one lung only, followed by selective ventilation of both lungs as described above.

ECG, arterial pressure, heart rate and frequency of breathing were monitored continuously throughout the study. Three horses were sacrificed by a large injection of barbiturate at the end of the study; the other two made an uneventful recovery from anaesthesia.

Statistics. The mean value and SEM were calculated for each variable under each condition. The Wilcoxon matched pairs signed rank test was used for testing the significance of a difference between different conditions.

RESULTS

In the standing horse, breathing air, Pa_{O_2} was normal and exceeded 13 kPa in all animals (fig. 5, table II). Pa_{CO_2} and pH also lay within the normal range (table II).

During anaesthesia in the lateral position, with the horse breathing spontaneously, Pa_{O_2} averaged 32 kPa (fig. 5). This should be compared with an inspired oxygen tension of approximately 90 kPa. Pa_{CO_2} was significantly increased and pH was reduced (table II). With the horse in dorsal recumbency, still with spontaneous ventilation, Pa_{O_2} decreased markedly—to an average of 11 kPa. This was significantly less than the awake value with air breathing. Pa_{CO_2} remained increased and pH remained reduced. The commencement of general mechanical ventilation in dorsal recumbency caused no significant change in Pa_{O_2}. Pa_{CO_2} was decreased and no longer differed from the awake value. pH was significantly increased and also reached the awake value.

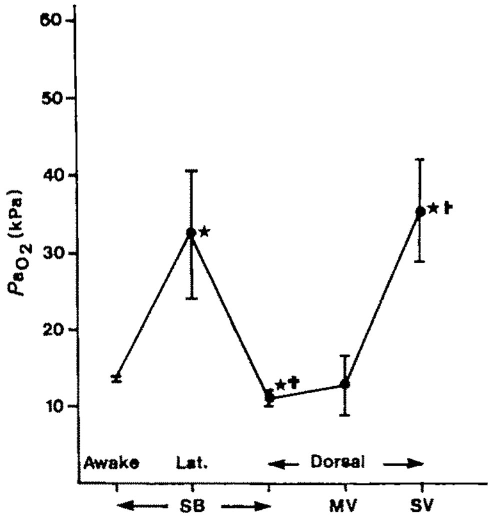


FIG. 5. Arterial oxygen tension (mean ± SEM) in the awake, standing horse, (FI_{O_2} 0.21), and during anaesthesia in the lateral and dorsal recumbent positions ($FI_{O_2} > 0.92$). SB = Spontaneous breathing; MV = general mechanical ventilation; SV = selective mechanical ventilation with PEEP 20 cm H_2O. *Significantly different from the awake value ($P < 0.05$); †significantly different from the previous value ($P < 0.05$).

When selective mechanical ventilation with PEEP 20 cm H_2O was added to spontaneous breathing, with the animal in dorsal recumbency, Pa_{O_2} increased markedly, reaching a value 3–3.5 times greater than during spontaneous or general mechanical ventilation in the same position (fig. 5). (The inspired oxygen tension was essentially the same as during the previous measurements during anaesthesia.) Pa_{CO_2} and pH did not change to any significant extent (table II).

Selective mechanical ventilation of dependent regions in only one lung, with PEEP ($n = 3$), increased Pa_{O_2} from a mean of 11.9 kPa (spontaneous breathing) to 21.8 kPa, and bilateral selective ventilation with PEEP increased Pa_{O_2} to

TABLE II. *Arterial blood-gas tensions (kPa) (mean ± SEM) and pH in awake and anaesthetized horses. For abbreviations, see text. Significant differences: *from the awake value; †from the above value* ($P < 0.05$)

	n	Pa_{O_2}	Pa_{CO_2}	pH
Awake (air)				
Standing, spontaneous breathing	5	13.6±0.2	6.4±0.5	7.36±0.03
Anaesthetized (>92% oxygen)				
Left lateral recumbency Spontaneous breathing	5	32.3±8.2*	8.4±0.5*	7.25±0.01*
Dorsal recumbency Spontaneous breathing	5	10.9±0.9*†	8.0±0.9*	7.25±0.04*
Dorsal recumbency General mechanical ventilation	4	12.6±3.9	5.7±0.4†	7.31±0.02†
Dorsal recumbency Selective mechanical ventilation	4	35.3±6.6*†	7.1±0.1	7.23±0.05

an average of 36.4 kPa. Thus unilateral selective ventilation had only a partial effect on Pa_{O_2}, compared with bilateral selective ventilation.

DISCUSSION

This study has shown that the great difficulties in oxygenating the anaesthetized horse in a dorsal recumbent position can be largely overcome by selective ventilation of, and application of PEEP to, the most dependent lung regions. Although only tested in preliminary studies this ventilatory technique appears promising and may be of clinical importance. Possible mechanisms underlying the improvement in pulmonary gas exchange, and comparisons with previous experience in man, are discussed below.

Distribution of ventilation

The marked improvement in arterial oxygenation that occurred on inflation and ventilation of the dependent lung regions strongly suggests that these regions had been collapsed or that the airways had been occluded, before selective ventilation. The morphological appearance of lung regions corresponding to the diaphragmatic dependent regions, with airlessness and congestion (fig. 2), is compatible with alveolar collapse rather than airway closure. In man, prompt development of atelectasis in dependent lung regions on induction of anaesthesia has been demonstrated (Brismar et al., 1985), as well as impairment of arterial oxygenation, which does not necessarily progress with time (Nunn, Bergman and Coleman, 1965). It has been suggested that the atelectasis may be caused by loss of supporting forces (compression atelectasis) rather than by resorption of gas from occluded lung units (Brismar et al., 1985; Strandberg et al., 1986). In a recent study in anaesthetized horses, Nyman, Funkquist and Kvart (in preparation) found that the impairment in pulmonary gas exchange could progress for more than 1 h in the dorsally recumbent horse. This time difference, as compared with man, may suggest additional or alternative explanations for the impairment in gas exchange. One possibility is resorption atelectasis; another is increasing vascular congestion. These mechanisms may aggravate a gas exchange impairment, initially caused by compression of lung tissue.

The ventilator used in the present studies had been constructed for use in anaesthetized, essentially healthy humans and was not able to maintain any greater degree of ventilation. This was at most 10–15 litre min^{-1} and can be expected to be 25% of the total ventilation, the remainder being produced by spontaneous breathing. This may have resulted in a ventilation per unit lung volume in dependent lung regions that was less than the average. However, inflation of dependent lung units with oxygen without any ventilatory movements will create effective oxygenation of the pulmonary capillary blood for a number of hours, the major problem being inefficient elimination of carbon dioxide (cf. the studies on apnoeic oxygenation by Holmdahl (1956)). However, since a major part of the total ventilation was created by spontaneous breathing, Pa_{CO_2} was determined by the sensitivity to carbon dioxide of the respiratory centre and not by the efficiency of the selective ventilation.

Distribution of perfusion

Since the impaired arterial oxygenation in the anaesthetized horse was observed during the breathing of almost 100% oxygen, contributions by diffusion limitation and ventilation–perfusion mismatching can be considered negligible. The poor oxygenation of blood must therefore have been caused by a large shunt, that is, a blood flow not coming into contact with ventilated lung tissue. This would fit with the idea of maintained blood flow in dependent, collapsed and thus non-ventilated lung regions. In studies on anaesthetized humans, shunts as large as 15–17% of the cardiac output have been observed, together with atelectasis no greater than 6–8% of the transverse intrathoracic areas, as measured by computerized tomography (Hedenstierna et al., 1986). The explanation for this may be that gravitational forces create a larger blood flow in the lowermost lung regions than in upper units (West, Dollery and Naimark, 1964). By this means, even small regions of occluded or collapsed dependent lung tissue may cause a considerable shunt. The vertical blood flow distribution in the horse lung may differ (Stolk, 1982), but as yet no detailed topographical analysis has been made.

Another question is whether the regional application of selective ventilation with PEEP forces blood flow away from this region. In anaesthetized, healthy humans placed in a lateral position, the dependent lung received approximately 60% of the total lung blood flow during mechanical ventilation with no end-expiratory pressure, and this decreased to 50% with selective PEEP of 10 cm H_2O to that lung (Hedenstierna et al., 1984). To what extent this result is applicable to the horse remains to be shown. However, it can be concluded that either mechanism—recruitment of collapsed lung tissue or redistribution of blood flow—should result in reduced shunting.

CONCLUSION

This study has shown that dependent regions of the diaphragmatic lobes of the lung can easily be intubated and ventilated by means of bronchial catheters introduced through a tracheostomy, and that selective ventilation of dependent lung regions, with PEEP, results in a more than three-fold increase in arterial oxygenation from a dangerously low to a high Pa_{O_2}. The ventilation technique described in this paper may prove to be one of choice for prolonged surgery in the anaesthetized, dorsally recumbent horse.

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AUTOTRANSFUSION: QUALITY OF BLOOD PREPARED WITH A RED CELL PROCESSING DEVICE

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SUMMARY

The quality of blood salvaged at operation and prepared with the Dideco Autotrans BT 795 autotransfusion device was compared with that of donor blood in 41 patients having cardiac surgery involving cardiopulmonary bypass. Saved blood had a higher haemoglobin concentration (17.3 v. 13.1 g dl^{-1}*;* $P < 0.001$*), a higher 2,3-diphosphoglycerate concentration (5.3 v. 1.1 mmol litre*$^{-1}$*;* $P < 0.00001$*), higher white cell count (*17.1×10^9 *litre*$^{-1}$ *v. 4.1;* $P < 0.00001$*), higher pH (7.5 v. 6.6;* $P < 0.00001$*) and a more physiological potassium concentration (5.4 v. 8.8 mmol litre*$^{-1}$*;* $P < 0.00001$*) than donor blood. Saved blood platelet count was* 34.5×10^9 *litre*$^{-1}$ *compared with* 146.24×10^9 *litre*$^{-1}$ *(*$P < 0.00001$*) and its heparin concentration was 0.64 u. ml*$^{-1}$*. We conclude that this autotransfusor is a useful aid to blood conservation, producing good quality red cells with relatively normal pH and potassium values. However, modification of the centrifugation and washing is required to lessen the high white cell count and heparin concentrations found in the saved blood.*

The use of homologous donor blood remains the most common form of blood replacement therapy in spite of the evergrowing list of attendant risks. To the risk of hepatitis, malaria, toxoplasmosis, cytomegalovirus infection and syphilis (Grady and Bennett, 1972; Collins, 1974) has recently been added the risk of acquired immune deficiency syndrome (Bove, 1984; Curran et al., 1984; O'Duffy and Isles, 1984). In addition to the above, recipients are also exposed to the possibility of isosensitization, febrile and graft *v.* host reactions, mismatching of blood, hyperkalaemia and hypothermia (Collins, 1974; Young, 1964). Furthermore, donor blood is acidotic and its red cells are depleted of 2,3-diphosphoglycerate (2,3-DPG) (Hogman, 1971; Valeri and Hirsch, 1969), making them less than ideal for their primary function—oxygen carriage and delivery.

In the surgical setting where blood transfusion is used mainly to replace perioperative loss, autotransfusion of shed blood is a possible alternative to donor blood. However, since it was first advocated by Highmore in 1874, autotransfusion in its various forms has enjoyed varying popularity. Tempering the enthusiasm of its advocates have been reports of haemolysis, coagulation disturbances, emboli, renal failure and pulmonary disturbances in autotransfused patients (Bell, 1978; Mattox, 1978; Sharp, Stark and Donovan, 1981). With the development, since 1976, of techniques capable of rapid washing and concentrating of red cells aspirated from the surgical field for reinfusion, many of these problems have been avoided. Nonetheless, autotransfusion is still not used very widely. This may be because of conflicting reports concerning the quality of autotransfusion blood. Conflict exists specifically with regard to whether heparin remains in the finished product (Umlas and O'Neill, 1981; Keeling et al., 1983), whether platelets remain (Orr, 1978; Moore et al., 1980; Saarela, 1981) and whether white cells remain (Orr, 1978; Ottesen and Froysaker, 1982). In an

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effort to elucidate some of these problems we studied blood produced by the Dideco Autotrans BT 795 (Dideco S.p.A., Mirandola, Italy), a red cell processing device. In addition to measurements of the concentration of heparin, and of the numbers of platelets and white cells, we measured haemoglobin, haematocrit, pH and concentrations of lysozyme, potassium and red cell 2,3-DPG, and compared these values with those in donor blood.

PATIENTS AND METHODS

Forty-one patients undergoing cardiac surgery involving cardiopulmonary bypass were selected randomly for the study. Twenty patients (12 male) aged 37–74 yr (mean 56.4) were assigned randomly to receive autotransfusion and, if necessary, homologous blood (saved blood group). Twenty-one patients (16 male) aged 15–64 yr (mean 47.76) received homologous blood only (donor blood group). In the autotransfused group, all peri-operative shed blood was aspirated into a reservoir, using a low pressure suction device (less than 100 mm Hg) to minimize haemolysis. This blood was heparinized by means of heparinized lactated Ringer's solution (heparin 30000 u. litre^{-1}), which was delivered continuously to the tip of the suction wand. The aspirated blood was stored in a cardiotomy reservoir where it was defoamed and filtered before being passed to the centrifuge bowl of the autotransfusion device. Here, it was centrifuged and washed with lactated Ringer's solution (1000 ml approximately) until the effluent or waste fluid was clear in colour. Thus the red cells were saved and plasma, debris and other cells discarded. These red cells were then suspended in lactated Ringer's solution and pumped to a transfusion bag for reinfusion to the patient. Samples were taken from this bag for measurement of the following: haemoglobin concentration, haematocrit, red cell count, mean corpuscular volume, lactic dehydrogenase and red cell 2,3-DPG concentrations; white cell count and lysozyme concentration; platelet count; pH and potassium concentration; heparin assay and blood film. The same studies, excepting a heparin assay, were carried out on the first unit of donor blood used in the homologous transfusion group of patients. Donor blood used in all cases was less than 1 week old (average 4.5 days) and had been preserved with adenine and acid–citrate–dextrose (ACD). Student's t test was used for statistical analysis of results.

RESULTS

The saved blood group of patients had coronary artery bypass grafting (eight patients), valve replacements (11 patients) and valve and coronary artery bypass grafting (one patient) performed. The donor blood group had coronary artery bypass grafting (16 patients), valve replacements (four patients) and repair of an atrial septal defect (one patient) performed. The time spent on bypass averaged 96.7 min (SD 37.4) in the saved blood group, and 77.5 min (SD 26.9) in the donor blood group ($P = 0.033$). All patients in both groups survived the immediate postoperative period after a variable length of stay in the intensive care unit (15–72 h). The average volume of saved blood per patient was 1350 ml (range 450–3150 ml). The results of haematological measurements are presented in tables I, II and III.

DISCUSSION

The finding of a high haemoglobin concentration, and high haematocrit and red cell count in cell saved blood is in accordance with the findings of others using similar devices (Ottesen and Froysaker, 1982; Keeling et al., 1983). These red cells

TABLE I. *Red cell findings (mean values ± SD). Number of patients in the saved blood group is 20 and in the donor blood group is 21, unless otherwise stated*

	Haemoglobin (g dl^{-1})	Haematocrit (%)	Red cell count ($\times 10^{12}$ litre^{-1})	Mean corpuscular volume (fl)	Lactic dehydrogenase (i.u. litre^{-1})	2,3-Diphosphoglycerate (mmol litre^{-1})
Saved blood	17.3 ± 2.9	52.5 ± 8.9	5.8 ± 0.9	90.9 ± 5.6	316.5 ± 97.7 ($n = 17$)	5.3 ± 1.2 ($n = 18$)
Donor blood	13.1 ± 4.4	42.7 ± 14.8	4.4 ± 1.5	96.4 ± 3.1	452.2 ± 231.7 ($n = 19$)	1.1 ± 0.6 ($n = 17$)
P	< 0.001	< 0.01	< 0.001	< 0.001	< 0.01	< 0.01

TABLE II. *White cell findings (mean values ± SD). Number of patients in the saved blood group is 20, and in the donor blood group is 21, unless otherwise stated. ns = not significant*

	White cell count $(\times 10^{9}$ litre$^{-1})$	Lysozyme (µg litre^{-1})	Neutrophils (%)	Intact neutrophils (Microscopy) (%)
Saved blood	17.1±8.3	9.0±5.7 ($n = 15$)	94.6	26.7±19.2
Donor blood	4.7±1.4	7.7±3.8 ($n = 19$)	57.7 ($n = 14$)	76.8±22.2
P	< 0.00001	ns		< 0.0001

TABLE III. *Miscellaneous findings (mean values ± SD). Number of patients in the saved blood group is 20, and in the donor blood group is 21, unless otherwise stated*

	Platelet count $(\times 10^{9}$ litre$^{-1})$	pH	Potassium (K^+) (mmol litre^{-1})	Heparin (u. ml^{-1})
Saved blood	34.5±23.8	7.5±0.11	5.4±0.3	0.6±0.3
Donor blood	146.2±89.8	6.6±0.06	8.8±2.1	—
P	< 0.00001	< 0.00001	< 0.00001	

were seen to have a normal mean corpuscular volume, while that of donor red cells was slightly above the upper limit of normal (95 fl), presumably as a result of osmotic swelling. The finding of lactic dehydrogenase in the saved blood, while within the maximal range for freshly drawn blood, indicates one of two things. Either the blood is not being washed adequately or the saved red cells are damaged and leak lactic dehydrogenase while sitting in the transfusion bag before return to the patient. The first of these explanations is the more likely, as we have other evidence that the washing procedure is inadequate, namely that a large amount of heparin was found in the saved blood after the washing cycle. Furthermore, there was no evidence that the red cells were damaged. Their appearance under microscopy was normal and, as others have found (Orr, 1978; Noon, 1978), they contained greater 2,3-DPG concentrations than donor blood. Other workers have shown also that red cells saved in this way have a normal survival time (Ansell et al., 1982) and increased resistance to osmotic stress (Orr, 1978).

The concentration of 2,3-DPG measured in saved blood was equal to normal controls, while that in donor blood was only 20 % of normal. The finding of such a low value in donor blood less than 1 week old (4.5 days) is surprising and is much lower than the 99 % claimed for donor blood at 1 week of storage (America Association of Blood Banks, 1981).

Transfusion of blood with a low oxygen affinity, implied by normal 2,3-DPG concentrations, is especially beneficial to patients weaned from coronary bypass, for a number of reasons. By shifting the oxygen dissociation curve to the right it facilitates oxygen delivery, and should thereby improve cardiac and cerebral function. Work on man and animals (Dennis et al., 1975; Valeri et al., 1975; Woodson, 1979), has confirmed a beneficial effect on both cardiac performance and cerebral function following such a shift in the curve. Furthermore, as donor red cells remain depleted of 2,3-DPG for up to several days after transfusion (Valeri and Hirsch, 1969; Hogman, 1971), the advantage to those who received cell saved blood may continue throughout the critical first few days after surgery.

The finding of high white cell counts, 95 % of which were neutrophils, in the saved blood is a worrying feature and is in contrast to other studies which found normal (Ottesen and Froysaker, 1982) or very low white cell counts (Orr, 1978). As neutrophils have been shown to play a pivotal role in the pathogenesis of adult respiratory distress syndrome (Editorial, 1984), transfusion of this blood may contribute to postoperative ventilatory complications. The fact that almost 75 % of these neutrophils were seen to be badly damaged on microscopy may amplify their potential damage. This may occur because these damaged cells may permit massive leakage of their many enzymes, including proteinase, which have been shown to be capable of degrading the structural components of lung interstitium as well as lung surfactant apoproteins (Janoff et al., 1979). The finding of lysozyme concentrations at the upper limit of the normal range in the saved blood indicates either inadequate washing of the blood or leakage from the white cells as they stood in the transfusion bag. If the latter is the case, the wory about the possible adverse effects of this white cell transfusion is very real. If, on the other hand, the lysozyme present was the result of inadequate washing of the blood (and there is evidence of this, (see above)) and not cell leakage, the risks may be less. However, as we did not measure other white cells enzymes, or sample for lysozyme estimation immediately after the wash cycle was complete, we are unclear, as yet, what the extent of the danger is. Furthermore, as we did not perform a detailed study of pulmonary function after surgery in the two groups of patients, the clinical significance of the problem remains uncertain.

Our finding of 34000×10^9 platelets per litre is somewhat similar to that of other workers (Ottesen and Froysaker, 1982) using a similar device, but differs from the finding of Orr (1978) of no platelets in similarly saved blood. Red cell saving devices are supposed to remove platelets (Saarela, 1981) and this has some theoretical advantages, as they have been exposed to surgical incisions and adenine disphosphate (ADP) from haemolysed red cells, both of which may precipitate unwanted platelet activity (Moore et al., 1980). The relatively high platelet count found in donor blood of 4.5 days old was unexpected (Walter and Oberman, 1981). However, we did not test those platelets for function and they may or may not contribute to useful haemostatis. Hyperkalaemia associated with the use of donor blood may have deleterious effects on cardiac rhythm (Young, 1964) and, being acidotic, it upsets the recipient's acid–base balance. The close to normal pH and potassium concentrations in saved blood are thus further advantages over donor blood.

The finding of heparin 0.64 u. ml^{-1} in the saved blood is more than three times the recommended safe value (Umlas and O'Neill, 1981) and is in stark contrast to studies which found little or no heparin in saved blood (Ottesen and Froysaker, 1982; Keeling et al., 1983). This occurred despite using in excess of the manufacturers' recommended minimal washing volume of 750 ml. As we measured acclerated clotting times routinely in patients being weaned from bypass to guide our reversal of systemic heparinization with protamine sulphate, the infusion of heparin with the saved blood does not represent a great danger in the cardiac setting, but could pose problems in other situations, such as massive trauma.

In conclusion, the Dideco Autotrans BT 795 yields a product with a high haemoglobin concentration, high haematocrit, normal mean corpuscular volume and normal red cell 2,3-DPG concentration. The pH and potassium concentration are close to the physiological range. Disquieting features include high white cell and platelet counts and a high heparin concentration.

Our findings report the qualitative aspects of salvaged blood prepared with a red cell processing autotransfusion device. What the effects of using such blood have on patient outcome is obviously of importance to all who may use such a device. With this in mind, we are currently studying the quantitative effects of the use of such blood on the requirement for donor blood, and its influence on postoperative haematological indices, including haemoglobin concentration, white cell counts, platelet counts and indices of coagulation.

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INHIBITION OF RAT FETAL METHIONINE SYNTHASE BY NITROUS OXIDE

AN IN VITRO *STUDY*

J. M. BADEN, M. SERRA AND R. I. MAZZE

SUMMARY

The effect of in vitro *exposure to nitrous oxide on rat fetal and maternal methionine synthase activity was investigated. Enzyme solutions were prepared from livers of fetuses and mothers on day 19 of gestation and exposed to air, 50% oxygen or 50% nitrous oxide in oxygen for periods up to 24 h. Normal activity of methionine synthase in the fetus was about 65% of that in the mother. Activity decreased by about 25% over 24 h when the enzyme was incubated at 37 °C in the presence of either air or 50% oxygen. Nitrous oxide produced a time-dependent decrease in activity which generally was similar for both fetal and maternal enzyme. After 24 h exposure to nitrous oxide, activity has decreased to 14 and 17% of fetal and maternal control values, respectively.*

Nitrous oxide administered to pregnant rats at the end of gestation inhibits both maternal and fetal hepatic methionine synthase in a concentration- and time-dependent manner (Baden, Serra and Mazze, 1984). Inhibition in the fetus, however, lags behind that in the mother and it is uncertain whether this difference is attributable to the time taken for the fetal concentration of nitrous oxide to reach the maternal concentration or whether there is an intrinsic difference between the fetal and maternal enzyme. To help answer this question, we have examined the inhibition of fetal and maternal methionine synthase by nitrous oxide *in vitro*. We also have made observations about the *in vitro* stability of the enzyme and the effect of oxygen on its activity.

MATERIALS AND METHODS

Nine timed-pregnant Sprague-Dawley rats weighing 200–300 g were obtained from the breeder (Hilltop Lab Animals, Chatsworth Ca. 91311) on day 15 of gestation. They were bedded on ground corn cob (Bed O'-Cobs, Anderson's Cob Division, Maumee, Oh. 43527) and housed in polypropylene cages with stainless steel lids. Food (Wayne Lab-Blox, Allied Mills, Inc., Chicago, Il 60951) and water were allowed *ad libitum*.

On day 19 of gestation, the rats were killed by exposure to 100% carbon dioxide. Maternal livers were removed, perfused with cold 1.15% potassium chloride, and immediately frozen in liquid nitrogen. Fetuses were delivered by Caesarean section and placed on ice for about 10 min to ensure complete insensibility. Livers of fetuses from each litter were then removed, pooled and frozen in liquid nitrogen.

At the time of the study, approximately 1 g of liver was thawed and homogenized in 5 ml of potassium phosphate buffer 0.05 mol litre^{-1} (pH 7.4) with a Brinkman Polytron homogenizer for 20–30 s at three-quarters speed. The resultant homogenate was centrifuged in a Sorvall RC2-B centrifuge at 20000 *g* for 80 min at 4 °C. The protein content of the supernatant was measured by a modification of the method of Lowry and co-workers (1951), and adjusted to 10 mg ml^{-1} by addition of potassium phosphate buffer.

In vitro exposures were carried out in capped, 13 × 100-mm silicon-coated test tubes containing

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0.5-ml aliquots of supernatant (protein 5 mg). The head space of each tube was filled with a 50% nitrous oxide–50% oxygen mixture. Concentrations of nitrous oxide and oxygen were measured at the beginning and end of exposure with a Miran 1A infra-red gas analyser and an Instrumentation Laboratory 401 oxygen analyser, respectively. Samples were incubated with gentle agitation for 15, 30, 45, 60, 90 or 120 min in a water bath at 37 °C. In addition, five maternal and fetal samples were incubated for 24 h. At the end of exposure, tubes were uncapped, flushed with air and the samples frozen immediately at −4 °C. Control samples were treated in exactly the same way except that they were exposed to 50% oxygen and 50% nitrogen. In a further study, maternal and fetal samples were incubated for 24 h at 37 °C with air alone, to determine the stability of the enzyme over this period.

Methionine synthase was assayed according to the method described by Koblin and colleagues (1982). A 200-μl total volume of the methionine synthase reaction mixture contained: sodium phosphate buffer 20 μmol (pH 7.4), mercaptoethanol 25 μmol, adenosine methionine 50 mmol, vitamin B_{12} 10 nmol, homocysteine 50 nmol (freshly prepared from the lactone form), methyltetrahydrofolate 120 nmol (1 μCi of $[5\text{-}^{14}C]$-MTHF), and 40 μl of either supernatant or phosphate buffer. Following incubation for 1 h at 37 °C, the reaction was stopped by the addition of 800 μl of cold distilled water. The resultant 1.0-ml mixture was layered on a Dowex 1-X8 anion exchange resin (200–400 mesh; chloride form) column, previously equilibriated with sodium phosphate buffer 0.1 mol litre^{-1} (pH 7.4). The eluate was collected after washing with 3 ml of buffer. An aliquot of eluate was mixed with Aquasol 2, 10 ml and counted in a Beckman LS330 scintillation counter. Methionine synthase activity was expressed as nmol of methionine produced in 1 h per mg of protein.

Enzyme concentrations in maternal and fetal liver at the same time point were compared using the Student *t* test. Values at different time points within the same group were compared using analysis of variance and Newman-Keuls *post hoc* test. The difference between the inhibition of maternal and fetal enzymes was analysed by calculating areas under the activity–time curves using the trapezoid rule and comparing them using the Student *t* test. $P < 0.05$ was considered significant.

RESULTS

Control methionine synthase activity in fetal liver was 65% of that in maternal liver (table I).

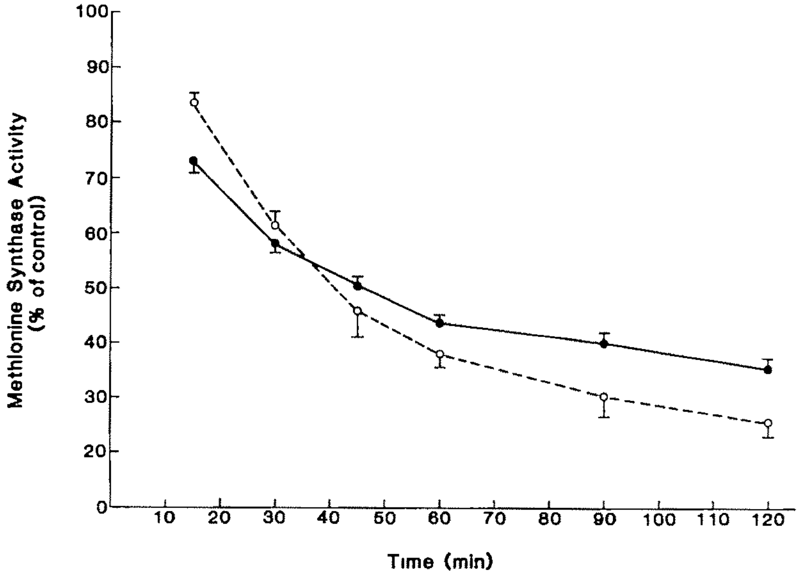

FIG. 1. Methionine synthase activity in fetal liver (open circles and dashed line) and maternal liver (solid circles and continuous line) following administration of 50% nitrous oxide and 50% oxygen. Each point is the mean ± SD for $n = 9$ rats.

TABLE I. *Methionine synthase activity (methionine nmol* h^{-1}*/mg protein) (mean ± SD) after 24-h exposure to air, 50% oxygen or 50% nitrous oxide. *Significantly less than control activity* (P < *0.01*)

		24-h Exposure		
	Control activity ($n = 9$)	Air ($n = 9$)	Oxygen ($n = 5$)	Nitrous oxide ($n = 5$)
Mother	1.90 ± 0.12	1.45 ± 0.10* (76%)	1.49 ± 0.35* (78%)	0.32 ± 0.03* (17%)
Fetus	1.24 ± 0.06	0.93 ± 0.06* (75%)	0.97 ± 0.04* (78%)	0.17 ± 0.04* (14%)

Activity in both fetal and maternal liver decreased progressively in a time-dependent manner following exposure to 50% nitrous oxide (fig. 1). The patterns of inhibition during the first 2 h of exposure were very similar. In particular, areas under the percentage activity–time curves during this period were not statistically different from each other. After 24 h exposure, activity was about 14 and 17% of fetal and maternal control activity, respectively (table I).

Concentrations of oxygen and nitrous oxide within the capped test tubes remained constant—even throughout the 24-h incubations. Also, there was no loss of activity of methionine synthase in frozen liver over the 3 months during which the studies were conducted. Even in diluted supernatant at 37 °C, the enzymatic activity decayed only slowly. After incubation for 24 h with gentle agitation at 37 °C in the presence of air, activity for both fetal and maternal enzyme was about 75% of initial activity (table I). A similar loss of activity was found after incubation with 50% oxygen under the same conditions, suggesting that this oxygen concentration had no inhibitory effect on methionine synthase.

DISCUSSION

When 50% nitrous oxide is administered to pregnant rats at the end of gestation, the time-dependent inhibition of methionine synthase in fetal liver lags considerably behind that in maternal liver (Baden, Serra and Mazze, 1984). For example, after 15-min exposure, activity of the enzyme decreases by 15% in fetal liver, but by 70% in maternal liver; a loss of 70% activity in fetal liver is achieved only after about 30 min. The most likely explanation for the difference is that equilibration to nitrous oxide is achieved more slowly in the fetus than in the mother and, therefore, the fetus is exposed to a lower average concentration. However, an alternative explanation might be that fetal and maternal enzymes are different or that the fetal enzyme is protected from the effects of nitrous oxide. Results from the present study support the equilibration hypothesis, since the difference between the pattern of inhibition of fetal and maternal methionine synthase was eliminated after *in vitro* exposure to nitrous oxide.

Methionine synthase proved to be fairly stable in dilute solution and was, therefore, easy to work with *in vitro*. After 24 h of incubation at 37 °C, only a 25% loss of activity was observed in untreated samples. Although the loss was small, it emphasizes the importance of running concurrent controls, especially if incubations are prolonged. Methionine synthase was not affected additionally by 24 h of incubation in the presence of 50% oxygen instead of air. This finding is consistent with that of other investigators (Sharer, Monk and Nunn, 1983) who found that hepatic methionine synthase activity in rats was unaffected by 4 h of exposure to two atmospheres of oxygen.

The significance of fetal exposure to nitrous oxide near the end of gestation has not been established. During routine Caesarean section, exposure probably is not long enough to decrease significantly the activity of methionine synthase. In a recent study, Landon and Toothill (1986) reported that methionine synthase activity in 11 placentae after Caesarean section during which nitrous oxide was administered, was not significantly different from that in 20 placentae after normal vaginal delivery. Exposure to nitrous oxide averaged less than 20 min. Our previous findings that exposure *in vivo* for 15 min did not significantly decrease enzyme activity in fetuses of rats (Baden, Serra and Mazze, 1984)—a species more sensitive to the biochemical effects of nitrous oxide than is man (Koblin et al., 1982)—is consistent with the data from the human placentae.

Longer exposure near the end of gestation would be expected to decrease fetal enzyme activity but, again, with uncertain consequences. Gross structural abnormalities would not be expected, and have not been reported, because the period of organogenesis is well passed. However, prolonged nitrous oxide administration is known to produce neurotoxicity in adult humans (Layzer, 1978; Brodsky et al., 1981). Animal studies have confirmed that the mechanism is a demyelination process resulting from an inadequate supply of methionine (Scott et al., 1981; van der Westhuyzen, Fernandes-Costa and Metz, 1982). Although neurotoxicity in adults occurs only after chronic exposure to nitrous oxide, the developing nervous system undergoing maturation, including myelination, may be sensitive to insult. Thus, a one-time exposure of fetuses to nitrous oxide could possibly induce discrete structural changes and result in neurobehavioural deficits. This was suggested in a review by Brackbill (1979), who noted that administration of inhaled anaesthetics, including nitrous oxide, to the mother at delivery was associated with poorer infant performance scores than was administration of local anaesthetics. However, most of the studies she reviewed were confounded by other factors which occurred at the time of delivery, such as the administration of additional drugs and the presence of underlying medical disease.

There is, however, experimental evidence from animals to suggest that nitrous oxide causes histological changes in the brain and neurobehavioural abnormalities. Cell proliferation in developing brains of mice exposed to 75% nitrous oxide for 6 h on day 14 of pregnancy showed some deviation from normal (Rodier et al., 1986). More significantly, exposure to nitrous oxide, but not to halothane, for 4 h on day 2 of the postnatal period produced a pattern of reduced cell proliferation followed by rebound that is characteristic of many antimitotic teratogens. Under the same conditions, long-lasting hypoactivity and behavioural deficits indicative of developmental neural damage occurred, although these effects were not unique to nitrous oxide, but were seen also with halothane (Koëter and Rodier, 1986; Rodier and Koëter, 1986). In another study, Rice and Millan (1985) exposed mice to 5, 15 or 35% nitrous oxide for 4 h per day on days 6–15 of pregnancy. Startle reflex hyporeactivity occurred in all exposed to nitrous oxide and was still present 3 months after delivery. Although these data are preliminary and not entirely unique to nitrous oxide, they point to the need for further clinical studies to determine whether nitrous oxide is a behavioural teratogen and, if so, whether inhibition of methionine synthase may play a role in this effect.

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DISTRIBUTION AND KINETICS OF ^{14}C-VECURONIUM IN RATS AND MICE

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SUMMARY

The distribution and kinetics of ^{14}C-vecuronium were studied in rats and mice. ^{14}C-Vecuronium accumulated rapidly in the liver. Both unchanged and metabolized vecuronium were excreted with the bile into the intestines and stomach. Reabsorption in the gut was probably responsible for an enterohepatic increase in radioactivity in the liver after one hour. Excretion through the kidneys increased continuously from low values after the initial peak. Binding in compartments with acid mucopolysaccharides such as cartilage, connective tissue etc., was less important. Blood–brain barrier and placenta were permeable only to a small degree.

Vecuronium-bromide is the monoquaternary analogue of pancuronium (Savage, Sleigh and Carlyle, 1980). Thus one might anticipate little change in activity because of this structural similarity or, alternatively, there could be a substantial decrease in neuromuscular blocking activity as with other monoquaternary compounds. Since the anaesthetist tends to use short-acting non-depolarizing neuromuscular blockers, vecuronium will be used extensively. As a result, its distribution to the organs, and its pathways of elimination, are of clinical importance.

MATERIALS AND METHODS

Animal preparation, drug application and sectioning

Twenty male rats were anaesthetized by the i.p. injection of 20% urethane solution (1.8 mg/g animal weight), a tracheostomy undertaken and artificial ventilation instituted via a tracheal tube. The ECG was monitored throughout. ^{14}C-Vecuronium bromide 6.76 μg g^{-1} (specific activity 2.39 mCi mmol $litre^{-1}$ = 3.7 μCi mg^{-1}) or 0.025 μCi/g animal weight, synthesized in our isotope laboratory by a special selective methylation technique (fig. 1), was injected via the tail vein. This dose is equal to seven times the LD_{100}. During the period of complete muscle paralysis artificial ventilation (48 b.p.m.: 95% oxygen: 5% carbon dioxide 4 ml) was maintained (Harvard rodent ventilator). At time intervals of 2, 5, 20, 60 and 120 min after injection, four animals from each of the five groups were killed by immediate immersion in a mixture of hexane/solid carbon dioxide (temperature −70 °C). The frozen animals were embedded in a gel of carboxymethyl cellulose (water–Na-CmC) and submerged in the cooling mixture and frozen to a solid block over 20 min. At six different levels, sagittal sections were cut (Cryo-microtome Type PMV-450, LKB, Stockholm) from the block, which was covered by broad scotch tape (3M). The undercutting produced tape-mounted sections of 20 μm

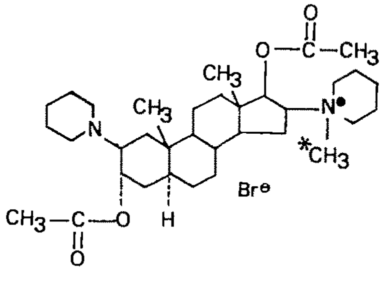

FIG. 1. Chemical structure of vecuronium. *Carbon-14 label.

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thickness. These were first dried for 3 days in the deep freeze, and autoradiographs were obtained. Corresponding sections were kept for histological staining and localization of radioactive tracers. The rest of the animal was stored in plastic bags in the deep freeze for radioactivity analysis by liquid-scintillation counting.

Whole-body autoradiography (*WBAR*)

The 20-µm mounted sections were covered by x-ray films (NS-25-No-Screen films, Eastman Kodak), and exposed for 16 weeks at −20 °C in the dark. The films were developed under standardized conditions. The densitometric evaluation of the degree of film blackening was achieved with a densitometer (TD-504 by Macbeth Kollmorgen). The evaluation of the degree of blackening of the films utilized a calibration scale which was obtained by simultaneous exposure of ^{14}C-glucose impregnated emulsion sheets on the films (Cross, Groves and Hesselbo, 1974). An exponential function for correcting the saturation of total film blackening was applied (Keller and Waser, 1982).

Liquid scintillation counting (*LSC*)

Samples of tissues or body fluids (20–200 mg) were taken out of the frozen animals, weighed and mixed with Soluene-100 1 ml (Packard) in vials, shaken on a 50 °C waterbath until completely dissolved after 3–5 h. Isopropanol 0.5 ml and 30% H_2O_2 0.5 ml were added and, after the exothermic reaction, mixed with Insta-Gel (Packard) and hydrochloric acid 0.5 mol litre^{-1} in a ratio of 9:1. These tissues were measured in a counter (Tricarb 3375, Packard). The correlation between ratio (R) and efficiency (E) was determined experimentally by determination of a quenching curve. As radioactive standard, ^{14}C-hexane (Amersham International Ltd) with a specific activity of 1.123×10^6 d min^{-1} g^{-1} was used.

Comparison between the results of densitometric determination (D) and liquid scintillation counting (L) of radioactivity was expressed as the ratio between the two relative standard deviations: $SD_{D:L}\%$.

Experiments with mice

Twelve male mice of average weight (24–27 g) were anaesthetized by i.p. injection of 20% urethane solution. ^{14}C-Vecuronium bromide 0.02–0.2 µCi g^{-1} was administered via a tail vein. The animals' lungs were ventilated artificially (95% oxygen, 5% carbon dioxide) via a tracheal cannula. The ECG was monitored and body temperature maintained at 36–37 °C. The animals were killed 2, 7 and 10 min after the i.v. injection, and immediately frozen. Eight pregnant mice, weighing 60–70 g, received ^{14}C-vecuronium 0.02 or 0.04 µCi g^{-1}. They were killed 2 or 5 min after the i.v. injection and frozen. The microtome sections were processed as described above, and the exposed films evaluated qualitatively but not quantitatively, because in this pilot experiment the doses given were very high, in order to produce positive autoradiographs.

RESULTS

Whole-body autoradiography (*rats*)

An immediate accumulation of radioactivity (after 2–5 min) occurred in the kidneys and liver (fig. 2). The liver concentration then decreased rapidly to one-third its original value by 20 min.

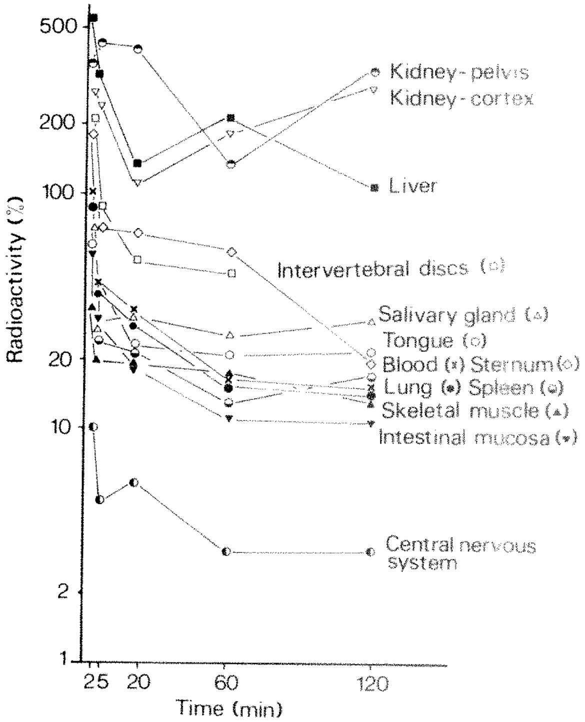

FIG. 2. Distribution of ^{14}C-vecuronium in rat organs at different times. Densitometric measurement of whole-body autoradiographs. Ordinate: radioactivity compared with concentrations in blood at 2 min = 100%. The elimination organs (liver, kidney) have most, the nervous system least radioactivity; intermediate concentrations of radioactivity in intervertebral discs and sternum.

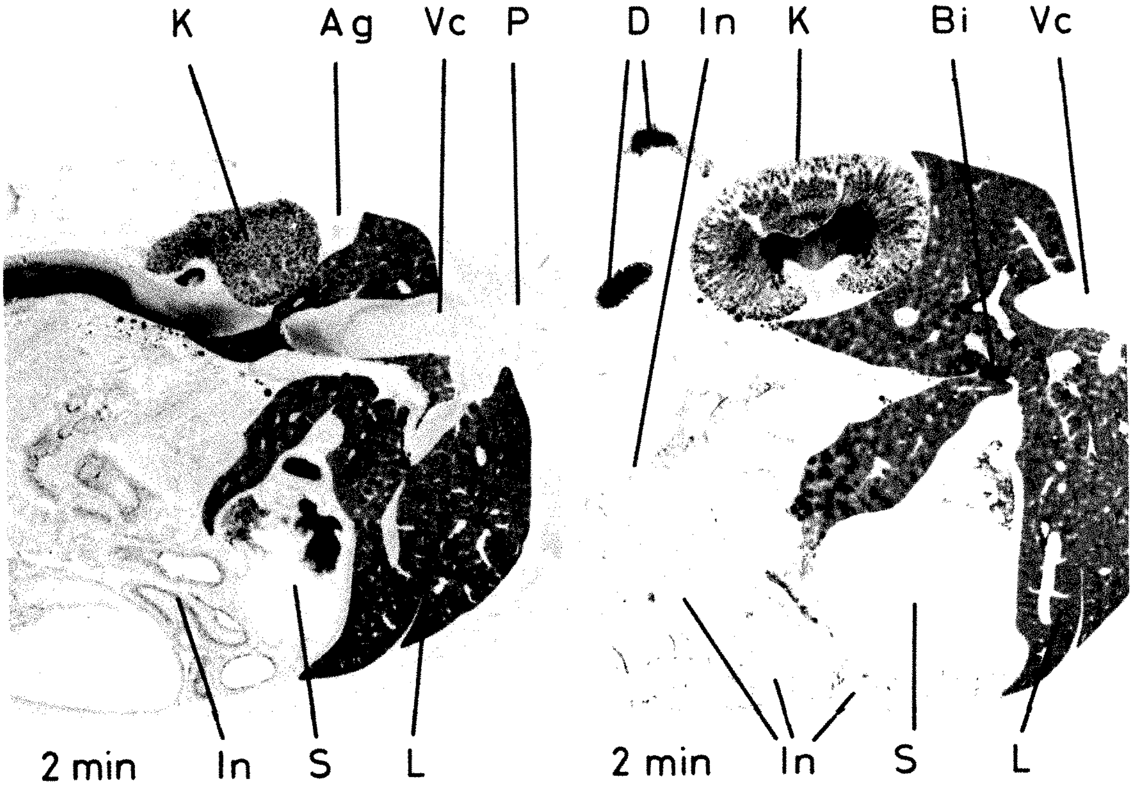

FIG. 3. Autoradiographs of section through liver, kidney, stomach, intestines, vena cava 2 min after i.v. injection of ^{14}C-vecuronium 0.025 μCi g^{-1}. The liver shows lobular structure with high radioactivity in the centre (central vein), and in the bile (ductus choledochus) entering the duodenum and stomach. The mucous membrane of the small intestine has little radioactivity. The kidneys excrete a large amount through their glomerulae and tubules into the kidney pelvis. Adrenal gland—no radioactivity. Ag = adrenal gland; Bi = bile; Bl = bladder; Br = brain; F = fetus; Gb = gall bladder; H = heart; ID = intervertebral disc; In = intestine; K = kidney; Kc = kidney cortex; Km = kidney medulla; Kp = kidney pelvis; L = liver; La = larynx; P = lungs; Pl = placenta; S = stomach; Sc = spinal cord; Sp = spleen; St = sternum; Vc = vena cava.

The autoradiography of liver tissue had a lobular aspect (figs 3, 4). The central veins of the lobules were mostly black for more than 20 min, and the liver cells remained uniformly dark for 2 h. At the same time the bile ducts were filled with highly radioactive bile.

The radioactivity of the renal cortex and medulla decreased simultaneously. The urine in the pelvis of the kidneys had a high concentration of radioactivity during the first 20 min which decreased slowly over the next 20–60 min.

A second period of increased radioactivity in the liver and kidneys followed after 20 min (fig. 5). The amount of ^{14}C-metabolites in the liver decreased after 60 min. Ample radioactivity was noted in the intestine. Radioactivity in the renal cortex, and in the urine in the pelvis of the kidney increased, over 60–120 min, demonstrating active excretion in the urine, measured in the kidney pelvis.

Much less radioactivity was found in the lungs, spleen, myocardium, skeletal muscle, bones, salivary and adrenal glands, and thymus, with a first peak 2 min after injection. The cortex of the adrenals had more radioactivity than the medulla. Very little radioactivity was observed in the central nervous system.

The blood ^{14}C-concentration followed an exponential decrease with three different phases (α, β, γ), in the same range as the mentioned organ activities (fig. 6). The bile—highly radioactive immediately after the injection—flows via

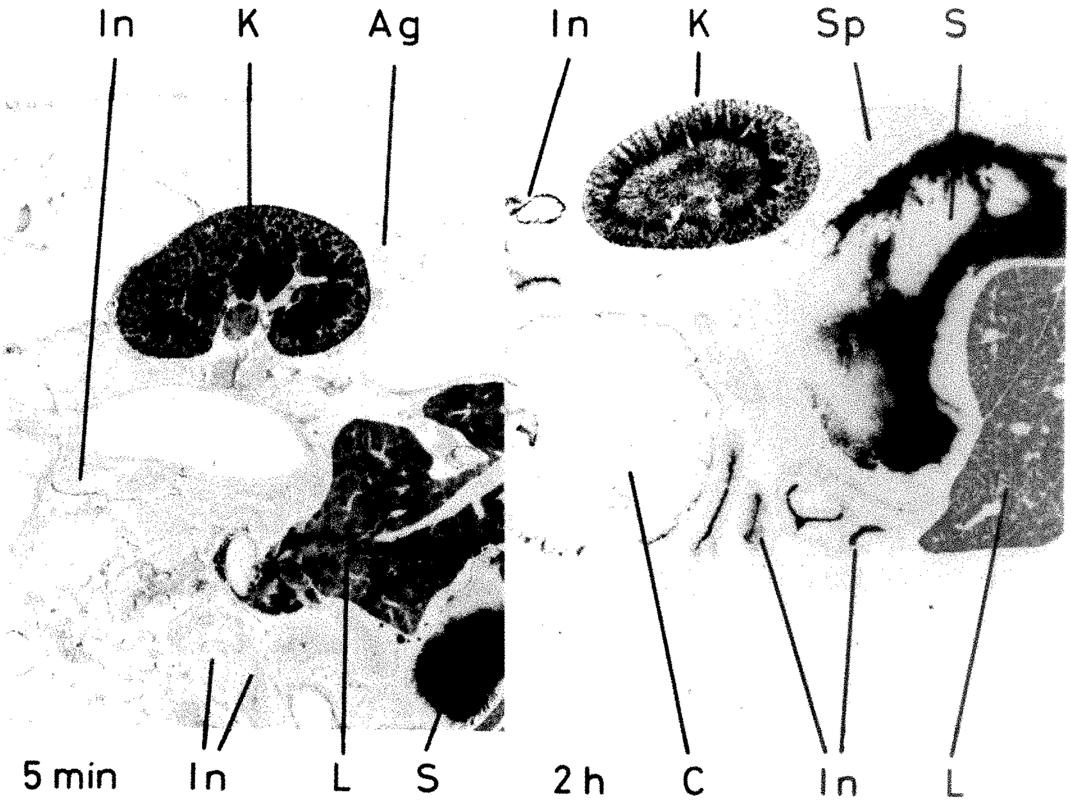

FIG. 4. Autoradiography of the same organs as in figure 3, 5 min (left) and 2 h (right) after i.v. injection. The liver tissue loses its lobular structure after 2 h, and more radioactivity has entered the intestines, but not the mucosa. The stomach is full of radioactive compounds; the kidneys are unchanged as before; adrenal gland is free of radioactivity. For key to abbreviations, see figure 3.

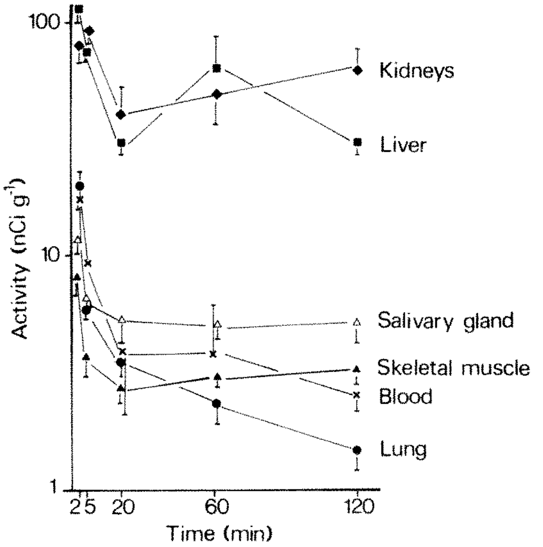

FIG. 5. Liquid scintillation counting of organ probes of the same rats show a similar distribution: high concentrations of radioactivity in kidneys and liver over 2 h, little in skeletal muscle and lung. Mean values ± SEM.

the bile duct to the duodenum, the intestines and the stomach. The radioactivity remained within the different parts of the intestines during the experiment and much of it was bound to the surface of mucous membrane and, perhaps, even absorbed.

In some tissues as cartilage of the sternum, intervertebral discs, snout, tendons and connective tissues, there was an immediate accumulation of considerable radioactivity—at first similar to that in the kidneys (fig. 7). However, the radioactivity decreased rapidly to average values within 20 min.

Distribution of radioactivity in mice

The distribution of radioactivity in the organs of mice was different than in rats. As mice are more sensitive to vecuronium than rats, the injected dose for autoradiography was relatively high, but proved useful for testing the permeability of the blood–brain and placental barriers. Two minutes after the i.v. injection of vecuronium the blood

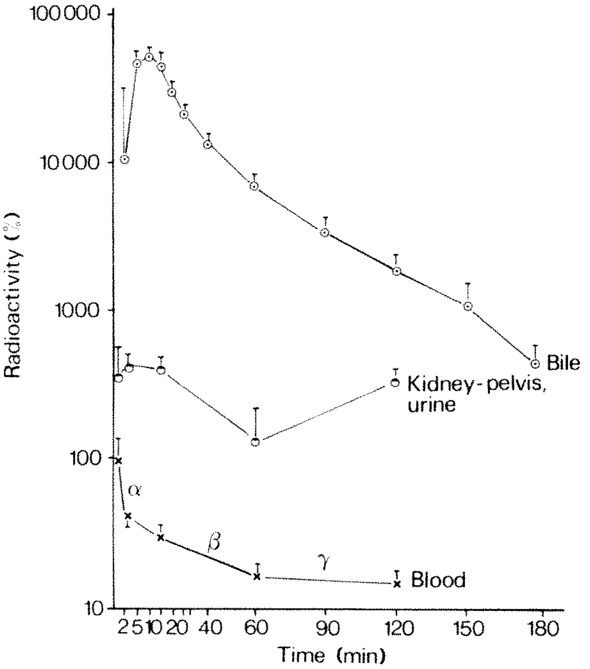

FIG. 6. The radioactivity (±SEM) of vecuronium and metabolites in the excretion fluids is much greater than in the blood. The concentration in the bile is nearly 1000-fold; in the urine, as measured in the kidney pelvis, 10-fold.

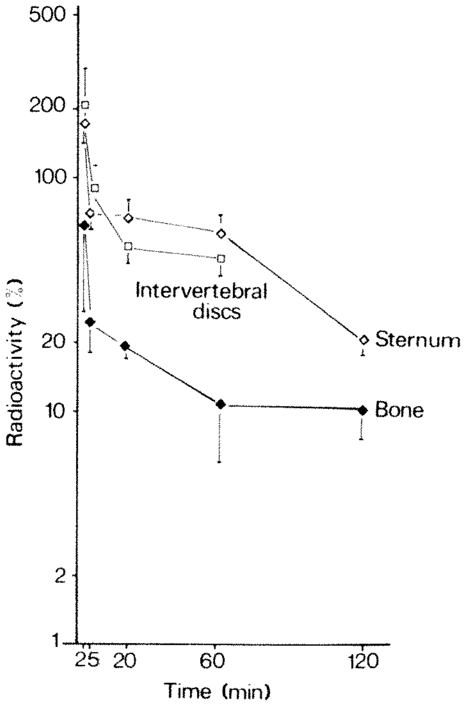

FIG. 7. As with other quaternary neuromuscular blockers, accumulation of positively charged drug molecules is detectable in the cartilage of bones in the vertebral discs, sternum, etc. It is less marked with vecuronium than with pancuronium. Vertical bars represent SEM.

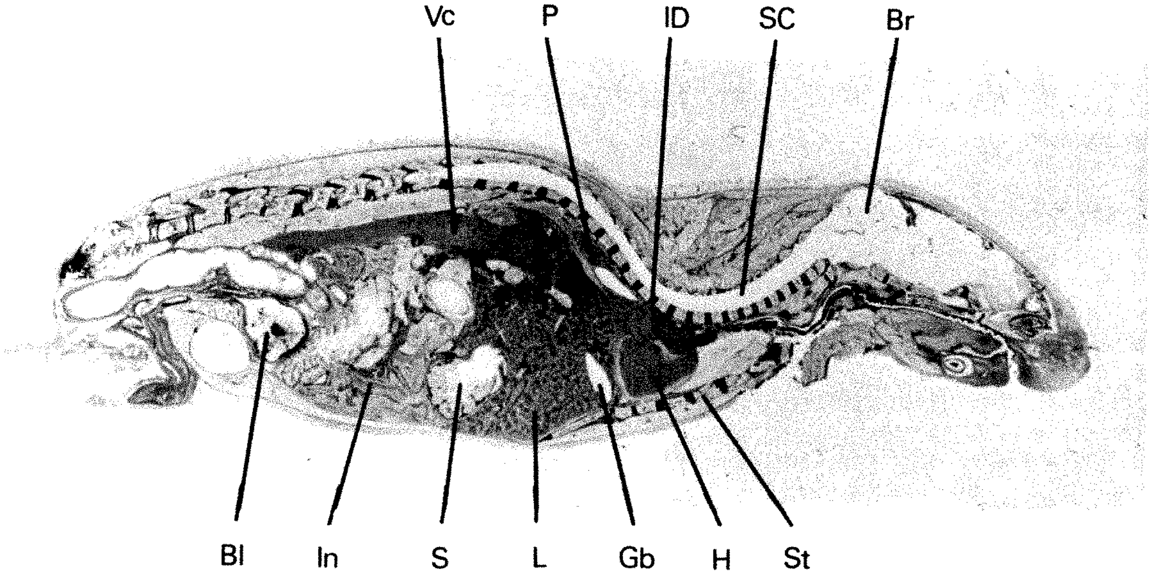

FIG. 8. Whole-body autoradiography of ^{14}C-vecuronium in a mouse, 10 min after i.v. injection of 0.025 μCi g^{-1}. The distribution in the organs is similar to that in the rat. Much radioactivity is already concentrated in the intervertebral discs, the sternum, the trachea and larynx. For key to abbreviations, see figure 3.

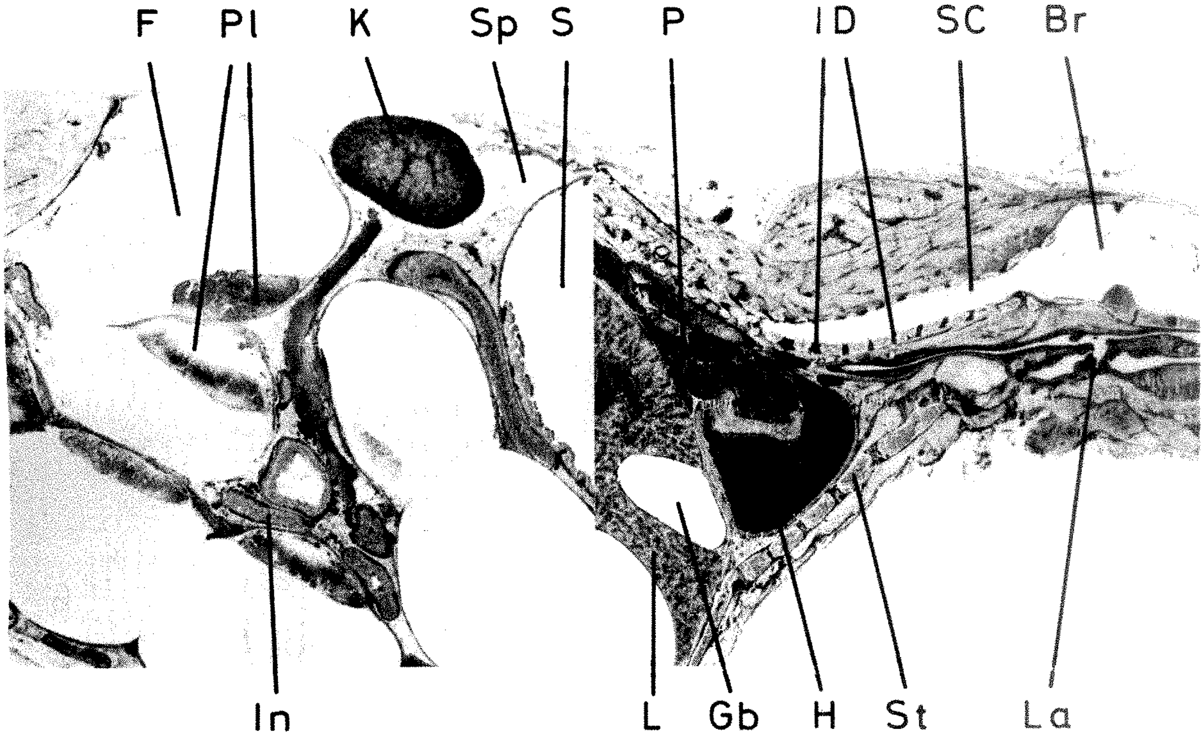

FIG. 9. Distribution in pregnant mouse 5 min after i.v. injection of 0.04 μCi g^{-1}. Even with a high dose, radioactivity is not detectable in the fetus, but is present in the placenta, with similar densities in the kidney, a renal vein and the intestinal mucosa. Intense radioactivity in the spinal column, sternum and larynx. For key to abbreviations, see figure 3.

was more radioactive than the liver tissue of male and pregnant animals. However, as radioactivity accumulated in the liver, both tissues had similar concentrations after 10 min. The bile contained little radioactivity and the gall bladder remained free of radioactivity. In contrast, the kidneys and the urine in the pelvis and in the bladder were darker than the liver, and the gastrointestinal tract contained (after 10 min) traces of radioactive material—mainly in the mucous membrane and partly in its lumen. There was no radioactivity in nervous tissues: only some of the blood vessels in the brain were blackened. The cartilage of joints, intervetebral discs, larynx and connective tissue became increasingly black within 10 min (fig. 8).

The placentae of pregnant animals were radioactive, similar to the intestines, but there were only slight traces of radioactivity in the fetuses (similar to the brain) (fig. 9). Even the livers of the embryos did not produce positive autoradiographs.

Liquid scintillation analysis of rat organs and mouse fetuses

The activities of a few typical uniform tissues and organs, measured by this method during the time course of the study, correspond largely with the densitometric measurements of the autoradiographs. However, no details of distribution in discrete small areas are recognizable. The comparison of the relative (%) values shows the close coincidence of the measurements by the two analytical methods.

Thirty minutes after i.v. injection (0.49 nCi/g animal weight) of ^{14}C-vecuronium to pregnant mice, the fetuses contained only 2.1% of the radioactivity of the injected dose per g tissue weight.

DISCUSSION

Based on the timing peaks of radioactivity in the various organs, we calculate that the distribution of ^{14}C-vecuronium is over 2 min after i.v.

injection. Blockade of neuromuscular transmission—with the 7 times LD_{100} dose (high, because this radioactivity is required for positive autoradiographs)—starts immediately but lasts, on average, only 10 min when one considers ventilatory movements. Thus onset time and duration of relaxation are shorter than with pancuronium (Durant, Houwertjes and Crul, 1980).

Vecuronium is metabolized in the liver and one metabolite, the 3-deactylated Org 7268, is excreted in bile and urine. We found only traces of this metabolite in the plasma. Therefore, the radioactivity in blood and organs, except the liver, is produced mostly by ^{14}C-vecuronium (Waser and Wiederkehr, in preparation).

Much radioactivity is extracted within the first 2 min by the liver and excreted through the bile into the intestines. The radioactivity in the stomach is probably the result of reflux from the duodenum. The radioactivity accumulated in the liver is 5 times greater than the blood concentration. Pancuronium, with an activity in the liver only 2 times greater than that in plasma after 60 min (Waser, 1973), is markedly different in its distribution, probably because of the more lipophilic character of vecuronium and its rapid metabolism in the liver cells. The second peak of radioactivity in the liver (between 20 and 60 min) may be attributable to reabsorption of ^{14}C-vecuronium excreted with the bile into the intestine, whereas the more hydrophilic metabolite will be excreted through the kidneys.

Lower concentrations of radioactivity were found in the kidneys at the start of distribution. After 5 min they were similar to those in the liver. The urine in the renal pelvis and in the bladder was strongly radioactive at the beginning of the excretion phase, then diminished and increased again after 60 min. This second wave of excretion followed the second liver peak. The total elimination through the kidney was not prominent at the start, but became important after 60 min.

There was an immediate uptake of vecuronium into different tissues containing acid mucopolysaccharides, such as cartilage, connective tissue, tendons. The uptake occurred immediately after the first pass of ^{14}C-vecuronium through the local circulation of these tissues (nucleus pulposus). Then the accumulation decreased rapidly—within the first 5 min—and then slowly in two stages over the next 60 min. The difference between the movement of other short-acting neuromuscular blockers (pancuronium (Waser, 1973), alcuronium (Waser and Lüthi, 1966)) into this storage compartment and that of vecuronium is evident, since with vecuronium it occurs early and is of short duration. The liberation of non-metabolized drug from these compartments into the blood stream will not prolong the neuromuscular blockade as this second inflow to the blood will be taken up immediately by the liver, where it will be partly metabolized and excreted through the bile.

The three kinetic phases of the radioactivity in plasma (fig. 10) can be explained as follows: α-phase—after the distribution by uptake into the liver and other organs or compartments as well as elimination through the kidney; β-phase—reappearance from the skeletal muscles and the mucopolysaccharide binding sites, again uptake into liver and metabolism producing more polar water-soluble metabolites; γ-phase—by the rest of vecuronium returning from the organs and water soluble metabolites being excreted now mainly through the kidneys.

During the early phases the extraction by the liver and the elimination of vecuronium and its metabolites with the bile are the most important of its kinetics. It is much greater than excretion

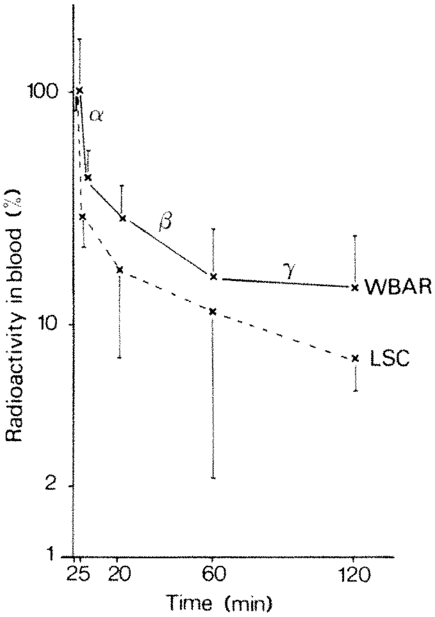

FIG. 10. The radioactivity (± SD) in the blood of ^{14}C-vecuronium and metabolite(s) measured with whole-body autoradiography and liquid scintillation counting diminishes in three phase (α, β, γ) in nearly identical manner.

through the kidneys and in the urine. With pancuronium, a bisquaternary highly polar compound, this proportion is reversed and in favour of elimination through the kidneys (Upton et al., 1982). The shifting of ^{14}C-vecuronium to the mucopolysaccharide-containing compartments (cartilage, connective tissue) is less important than with pancuronium. The relatively short duration of muscle relaxation produced by vecuronium is mostly the result of its rapid elimination, plasma binding (60–80%) and high extraction into the liver.

The pilot experiments in mice demonstrated some differences in the distribution of radioactivity compared with the rats. Some minutes after the injection of ^{14}C-vecuronium, the clearance of blood from the liver was smaller, and the kidneys and the urine contained more radioactivity. This may be because of the high injected doses. After 10 min this relation was partly reversed, and in the pregnant animals became at least equal. The intestines contained large amounts of radioactive bile, but the urine continued to be the main pathway of elimination. Possibly, in pregnancy, the elimination pathway through the liver–bile system is used less than in normal animals. There is a difference between rats and mice, as there was little radioactivity in the bile ducts of the latter, and the gall bladders were free of radioactivity.

Finally, the central nervous system with plenty of lipids in its membranes and neurones, contained very little ^{14}C-vecuronium. The passage through the blood–brain barrier, as through the placental barrier, is very limited; indeed, it is virtually zero (Demetriou et al., 1982).

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PHENOTYPING OF INDIVIDUALS SENSITIVE TO SUXAMETHONIUM

The Cholinesterase Research Unit at the Royal Postgraduate Medical School

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SUMMARY

Four hundred and thirty blood samples from suxamethonium-sensitive individuals have been phenotyped by the Cholinesterase Research Unit following its transfer from Exeter to the Hammersmith Hospital. The distribution of genotypes has been shown to be similar to that found in Exeter. Screening for the E_1^k *and* E_1^j *genes has not yielded any major differences in the gene frequencies of sensitive individuals, even during pregnancy. The uneven sex distribution of the patients, as well as other unusual points that have arisen, are discussed. A new gene for the biosynthesis of cholinesterase has probably been identified.*

It is 2½ years since the routine phenotyping for the cholinesterase variants occurring in individuals believed to be sensitive to suxamethonium was transferred from Exeter to the Royal Postgraduate Medical School, Hammersmith Hospital. An analysis of the distribution of variants occurring in these sensitive individuals is desirable, not only for comparison with earlier surveys, but also to ascertain the impact that the recognition of the E_1^k and E_1^j genes has made. These rare genes could be especially important in pregnant patients who are sensitive to suxamethonium. An unexpectedly high proportion of patients with the heterozygote, $E_1^uE_1^a$, appear to have a period of apnoea during Caesarean section (Whittaker, 1980). In this Unit, screening for the E_1^k and E_1^j genes has become routine practice, in spite of the fact that these genes can be recognized with confidence only when occurring as the heterozygotes with an E_1^a gene or when confirmed by family studies.

MATERIALS AND METHODS

All blood samples were phenotyped by determining dibucaine (DN) and fluoride (FN) numbers using benzoylcholine as substrate (Whittaker, 1977). The RO2-0683 (dimethylcarbamate of (2-hydroxy-5-phenyl-benzyl)trimethylammonium bromide) inhibition characteristics were assayed at 25 °C, in duplicate, using benzoylcholine 5×10^{-5} mol litre^{-1} as substrate and RO2-0683 10^{-8} mol litre^{-1} as differential inhibitor. The method was a modification of that described by Liddell, Newman and Brown (1963), but identical to that used by Evans and Wardell (1984).

RESULTS

The distribution of genotypes found in patients referred to the Unit during the 2½ years at the Hammersmith Hospital is given in table I. This table includes an analysis of samples sent to Exeter during this period as well as the distribution of genotypes during the year before the transfer of the Unit. An estimate of the gene frequencies of the patients phenotyped during the 2½-year period is given in table II.

Table III records the genotypes found in pregnant patients reported in the two later surveys recorded in table I.

DISCUSSION

It is apparent from the data given in table I that there was no significant change in the distribution of genotypes found in the three surveys. Some differences did occur, but these can readily be explained by the low frequencies of the rare genotypes.

There was, however, an uneven sex distribution

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TABLE I. *Distribution of genotypes in suxamethonium-sensitive individuals. NT = Not tested*

	Hammersmith		Exeter		Total		Exeter (1982)	
Genotype	No.	%	No.	%	No.	%	No.	%
$E_1^uE_1^u$	139	32.3	52	23.3	191	29.2	101	35.6
$E_1^uE_1^a$	103	24.0	44	19.7	147	22.5	44	15.5
$E_1^uE_1^f$	5	1.2	9	4.0	14	2.1	4	1.4
$E_1^aE_1^a$	77	17.9	53	23.8	130	19.9	68	23.9
$E_1^aE_1^s$	49	11.4	16	7.2	65	10.0	15	5.3
$E_1^uE_1^s$	21	4.9	25	11.2	46	7.0	39	13.7
$E_1^aE_1^k$	19	4.4	4	1.8	23	3.5	NT	NT
$E_1^aE_1^f$	7	1.8	10	4.5	17	2.6	6	2.1
$E_1^aE_1^j$	2	0.5	4	1.8	6	0.9	NT	NT
$E_1^fE_1^f$	1	0.2	2	0.9	3	0.5	1	0.4
$E_1^fE_1^s$	1	0.2	0	—	1	0.2	0	—
$E_1^sE_1^s$	5	1.2	3	1.3	8	1.2	6	2.1
Odd	1	0.2	1	0.4	2	0.3		
Total	430		223		653		284	

TABLE II. *The gene frequencies of the cholinesterase variants found in suxamethonium-sensitive individuals, sensitive pregnant patients and normal healthy controls in a British population. NT = Not tested*

		Gene frequencies					
	No.	E_1^u	E_1^a	E_1^f	E_1^k	E_1^j	E_1^s
Suxamethonium-sensitive individuals	653	0.4510	0.3193	0.0291	0.0176	0.0046	0.1753
Sensitive pregnant patients	65	0.4000	0.3385	0.0538	0.0231	0.0077	0.1769
British population	1516	0.9664	0.0148	0.0069	0.0119	NT	NT

TABLE III. *Distribution of genotypes in pregnant patients who are sensitive to suxamethonium or have a family history of sensitivity to the drug*

		Genotypes									
	No.	$E_1^uE_1^u$	$E_1^uE_1^a$	$E_1^uE_1^f$	$E_1^uE_1^s$	$E_1^aE_1^f$	$E_1^aE_1^k$	$E_1^aE_1^j$	$E_1^aE_1^a$	$E_1^aE_1^s$	$E_1^sE_1^s$
Sensitive patients (Hammersmith)	27	5	11	—	2	—	1	—	6	2	—
Sensitive patients (Exeter)	38	5	6	4	9	3	2	1	5	2	1
Patients with family history (Hammersmith)	31	11	9	1	7	—	1	—	—	2	—

in all the studies and, in fact, more than twice as many females as males occurred in the sensitive individuals. One must query whether the population for routine surgery is similarly weighted. In addition, one must ascertain whether the effect of pregnancy or the more widespread use of oral contraceptives, both of which are known to reduce plasma cholinesterase activity (Whittaker, 1986), are plausible explanations for this sexual imbalance. Leighton and colleagues (1986) have studied suxamethonium pharmacodynamics in peripartum patients. They used a peripheral nerve stimulator to determine the time from the injection of suxamethonium to 25% twitch height recovery among control patients, non-pregnant patients taking oral contraceptives, term-pregnant patients and postpartum patients. A similar duration of action of suxamethonium was found in the first three groups, but a slower recovery was observed in the postpartum patients. These results, obtained from women having the usual phenotype, $E_1^uE_1^u$, imply that neither pregnancy nor oral contraceptives are the causes of our observed sexual imbalance in the $E_1^uE_1^u$ sensitive individuals. A similar study has not been reported for the rarer genotypes.

The genotypes $E_1^aE_1^a$ and $E_1^aE_1^s$ are universally acknowledged as the principal categories of individuals sensitive to suxamethonium. The sensitivity of individuals having these atypical enzymes will be influenced neither by pregnancy nor by intake of oral contraceptives, since these enzymes do not hydrolyse the drug (Kalow, 1959). Analysis of the sex distribution of these genotypes in our three surveys should, therefore, give a better index of the surgical populations. Some sexual imbalance persists—albeit considerably smaller than found in our total surveys (F:M = 1.3). It is gratifying to find that, in one group of hospitals, the number of anaesthetics by sex classification during 1 year was 13695 female and 10329 male. We have not contacted other groups for their comparable statistics.

The frequency of the atypical phenotype ($E_1^aE_1^a$ and $E_1^aE_1^s$) is about 1 in 1800 and this can be used to give an approximate estimate of the number of anaesthetics which our service has covered during the past 3½ years. The number of atypical phenotypes recorded in table I is 278, so that an estimate of the number of anaesthetics covered by our surveys is 500400 or about 143000 per annum.

It is apparent from the data in table II that pregnancy produces no major distortion in the gene frequencies found in suxamethonium-sensitive individuals. This is somewhat surprising since the $E_1^aE_1^k$ heterozygotes have a mean enzymic activity lower than that of the $E_1^uE_1^a$ heterozygotes (Rubinstein, Dietz and Lubrano, 1978). It was assumed, therefore, that the risk of susceptibility to suxamethonium was greater in the $E_1^aE_1^k$ genotype than in $E_1^uE_1^a$ individuals and especially in the pregnant patient (Evans and Wroe, 1980). Our results do not at present uphold this hypothesis. However, it is difficult to produce a rational explanation for the high proportion of usual phenotypes referred as sensitive to suxamethonium during pregnancy. All have reduced enzymic activity, but one must query whether the universal use of a nerve stimulator would reduce this high proportion of usual phenotype in our surveys. In many cases the patient was being over-ventilated and the resulting apnoea was, presumably, the result of hypocapnoea. Central ventilatory depression will also produce a period of apnoea which may be mistaken for sensitivity to suxamethonium. Also, the steroid hormones associated with pregnancy may become attached to the cholinesterase molecule so that the resulting steric hindrance effect could retard the hydrolysis of suxamethonium by partial blockade of the active site of the enzyme to suxamethonium in some pregnant patients.

We are often asked whether it is worthwhile for a busy anaesthetist to screen the relatives of a suxamethonium-sensitive individual. At Hammersmith, 154/430 individuals have been followed up with family studies. At present 739 relatives have been screened and 333 individuals have been issued with sensitivity cards. This is a considerable improvement on the response of our early days with the Unit (Whittaker and Vickers, 1970). It is desirable to screen the siblings, parents and children of a sensitive individual. Few anaesthetists screen the siblings, who are often domiciled in a different area, but we have found that general practitioners will frequently assist by taking blood samples from relatives.

The purpose of a Reference Unit such as the one at Hammersmith is not only to provide reliable methodology for the phenotyping of the cholinesterase variants but to quote, on demand, the biochemical findings of any patient referred to us for phenotyping. In support of this service to anaesthetists we issue sensitivity cards only to individuals phenotyped in our laboratories. Each laboratory must establish its own range of variables for each genotype. We have observed a wide scatter of variables in different laboratories, even when the same method is used with basically similar conditions, and an interlaboratory study of cholinesterase phenotyping has shown many deficiencies in techniques (Evans, Wardell and Rapier, 1983). Greater difficulties are apparent when the experimental procedures are changed.

It is occasionally difficult or impossible to assign a genotype to an individual from the biochemical measurements. We have found two such individuals and confirmed our findings by repeat samples. The unusual phenotype found at the Hammersmith Hospital has had considerable family backup and our results are indicative of a new gene E_1^h, the Hammersmith gene, controlling the biosynthesis of plasma cholinesterase. Several members of the family had DN and FN values characteristics of $E_1^aE_1^a$, but very unusual RO2 numbers were invariably obtained. A detailed analysis of this family will be published elsewhere. It is only with the assistance of practising anaesthetists that we are able to show the existence of additional genes for cholinesterase.

The enzyme is stable and withstands the rigours of the British postal service at normal temperatures. Ten-millilitre samples of heparinized (or whole) blood from individuals showing an unusual reaction to suxamethonium should be sent, by first class post, to The Cholinesterase Research Unit in the Department of Anaesthetics at the Postgraduate Medical School, Hammersmith Hospital, London W12 0HS. Separated plasma or serum is much appreciated. It is desirable to have a record of the duration of apnoea as well as the patient's diagnosis to aid future analysis. In these days of computing patients records, it is mandatory to record a patient's sensitivity to suxamethonium. That this is not universal practice, is indicated by repeat samples from the same patient requested by the same hospital during successive pregnancies.

ACKNOWLEDGEMENTS

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MONITORING OF AXILLARY ARTERIAL PRESSURE IN A PATIENT WITH BUERGER'S DISEASE REQUIRING CLIPPING OF AN INTRACEREBRAL ANEURYSM

O. F. YACOUB, J. H. BACALING AND M. KELLY

SUMMARY

A 45-yr-old male with advanced Buerger's disease required surgical clipping of an intracerebral aneurysm. This case report emphasizes considerations of arterial pressure monitoring in a patient with advanced Buerger's Disease requiring a major surgical intervention.

CASE HISTORY

A 45-yr-old, 85-kg, previously healthy male patient was scheduled for clipping of an anterior communicating artery aneurysm diagnosed by CAT scan and arteriograms. The patient's main complaint was frequent headache, increasing in severity. He denied episodes of seizure, stroke or trauma; he had been a smoker for 20 years. The patient was known to have Buerger's disease and had undergone three surgical procedures during the previous 10 years: a right transmetatarsal amputation, an amputation of the right second and third fingers, and an aorto–bifemoral bypass with lumbar sympathectomy.

At the time of the pre-anaesthetic evaluation, the right dorsalis pedis pulse was noted to be absent. The other peripheral pulses were intact. Each radial artery was palpable, but diminished. Allen's test demonstrated poor collateral circulation in each hand.

Before the induction of anaesthesia, a continuous left brachial plexus blockade was performed using the axillary approach with a non-tapered 20-gauge, 32-mm Critikon catheter inserted tangentially to the skin. After paraesthesia was obtained, the stylet was removed and an extension tube filled with 0.5% bupivacaine was attached to the catheter and 30 ml of local anaesthetic injected. The catheter and tubing were taped securely. Fifteen minutes after the injection of the local anaesthetic, the patient experienced a sensation of "warmth" in the left hand. At this time, both ulnar and radial pulses were strong and the hand felt warmer. Venous dilatation was obvious and pin-prick sensitivity was diminished over the whole hand and arm. At this time, a left axillary artery catheter (20 guage) was inserted percutaneously. The catheter was 12.7 cm in length and was obtained from a paediatric central venous pressure tray. The arterial catheter was attached to a transducer and the arterial pressure displayed on an oscilloscope.

After preoxygenation, anaesthesia was induced with thiopentone 400 mg i.v. followed immediately by pancuronium bromide 10 mg i.v. to facilitate tracheal intubation. Anaesthesia was maintained with nitrous oxide, oxygen, isoflurane and fentanyl. The operative procedure lasted 9 h and 30 min. Vital signs were stable throughout. The left hand was observed continuously to detect changes in colour or temperature. A warming blanket, heated in-circuit humidifier and heat lamp were used to maintain body temperature greater than 37 °C. Six hours after the initial brachial plexus blockade, a second administration of 0.25% bupivacaine 30 ml was given. The patient was transferred to the neurosurgical intensive care unit, with the brachial artery and brachial plexus block catheters in place. Both catheters were removed 28 h after insertion. The trachea was extubated the following day. No

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additional brachial plexus blockade was performed and examination of the left arm and hand remained unremarkable. The patient recovered promptly and was discharged on the 6 day after operation, without sequelae.

DISCUSSION

The patient described emphasizes consideration of the risks and benefits of inserting an indwelling arterial line in a patient with known pathology of the arterial system. Buerger's disease is a peculiar form of occlusive disorder of the peripheral arteries in young males. It is a disease which primarily affects the small- and medium-sized vessels of the extremities. The disease begins peripherally and reaches the forearm or infrapopliteal arteries within a short time after the onset of symptoms. Proximal extension of the arterial occlusion is infrequent. The aetiology of Buerger's disease remains unknown. Tobacco seems to be a predominant associated factor and its contribution to the evolution of the disease in this patient is obvious (Bollinger et al., 1983; Shionoya, 1983).

Cerebrovascular involvement in Buerger's disease is infrequent, but clinical and pathological evidence can occasionally be found (Drake, 1982). In this patient, it seemed to be coincidental.

Cold and trauma are associated with vasospasm and exacerbation of the disease process. During this operative procedure, we were successful in maintaining the patient's rectal temperature at more than 37 °C with an electric warming blanket, heated in-circuit humidifier and warming lamp.

In patients with Buerger's disease, arterial pressure is ideally monitored with a Doppler sensor. Arterial catheterization is not usually recommended. The value of Allen's test is somewhat contested, but no patients with Buerger's disease were included in a large previous study of 1699 patients (Slogoff, Keats and Arlund, 1983). However, because of the nature of this surgical procedure, intra-arterial monitoring was chosen as permitting better control of arterial pressure and the withdrawal of blood samples for frequent blood-gas analysis.

The risks of indwelling intra-arterial catheters are well known (Bedford and Wollman, 1973; Abadis and Ung, 1980). Permanent ischaemic injury, the most significant complication, is rare and usually associated with previous arterial injury, hypotension, use of a vasoactive agent, prolonged cannulation, left heart embolization or severe infection (Michaelson and Walsh, 1970; Matthews and Gibbons, 1971; Samaan, 1971; Brown et al., 1984).

Axillary arterial cannulation has a record of safety and was chosen for intra-arterial pressure monitoring because of the proximal location of the artery (Rosenblatt et al., 1979). It allowed the continuous monitoring of arterial pressure in this patient.

In the patient described, hypotension was of great concern. After discussion with the surgeon, the decision was made to use minimal reduction in arterial pressure during the clipping of the aneurysm. Therefore, mean arterial pressure was kept between 65 mm Hg and 70 mm Hg during the clipping of the aneurysm and allowed to increase to the patient's normal mean of 80–85 mm Hg thereafter. The brachial plexus block was performed in this patient in order to protect the arm by increasing peripheral blood flow through a pharmacological sympathectomy (Selander, 1977). A continuous block was selected to provide an effect commensurate with the duration of surgery and the early postoperative period, and to minimize the dose of local anaesthetic required (Selander, 1977; Sada, Kobayaki and Murakami, 1983).

In summary, the management described illustrates that intra-arterial pressure monitoring can be performed in a patient with Buerger's disease requiring intracranial aneurysm surgery. Success in the technique selected can be attributed to the brachial plexus block and resultant pharmacological sympathectomy, maintenance of core body temperature and selection of the axillary artery for cannulation.

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MASSIVE INTRAOPERATIVE PULMONARY EMBOLISM IN A CHILD

N. W. GOODMAN AND M. J. FALKNER

SUMMARY

An 11-yr-old girl suffered a massive pulmonary embolus during an operation to insert an artificial bladder sphincter. Forty minutes after the induction of anaesthesia, the heart rate increased and she became hypotensive and deeply cyanosed. A definitive diagnosis was not made during surgery, but she improved after 45 min of resuscitation with 100% oxygen, infusion of normal saline, ephedrine (total 45 mg) and intermittent external cardiac massage. The diagnosis was proved the next day by lung perfusion scan. There were no apparent risk factors.

Pulmonary embolism is rare in children. However, it can occur, as in adults, in the postoperative period—especially after operations to correct scoliosis (Behrman and Vaughan, 1983). Other general risk factors include: severe dehydration caused by diarrhoea, cyanotic heart disease, and ventriculo–atrial shunts for hydrocephalus (Buck et al., 1981). We report a case of pulmonary embolism occurring in an 11-yr-old child *during* an operation to insert an artificial bladder sphincter.

CASE REPORT

An 11-yr-old girl, weighing 37 kg, was admitted for the elective insertion of an artificial bladder sphincter. She had had a sacral myelomeningocoele diagnosed at birth. Later she developed hydrocephalus secondary to an Arnold–Chiari malformation and a ventriculo–atrial valve was inserted initially. This was replaced with a ventriculo–peritoneal shunt 3 years before the current admission. She had developed normally and was doing well at school. She had had two orthopaedic operations and was fully ambulant. Her major disabilities were incontinence of urine and faeces.

At the time of admission, the patient was well. There were no new abnormal findings on physical examination, and the results of laboratory investigations were normal. There was no reason to request a preoperative electrocardiogram or chest radiograph. Her mother knew of no problems that had occurred during any of her previous anaesthetics. The child was taking nitrofurantoin, probanthine and codeine phosphate, and imipramine 25 mg at night. Sodium picosulphate (Picolax, Nordic) was given for bowel preparation.

Temazepam was given 10 mg orally 90 min before the induction of anaesthesia, during which fentanyl 100 μg, thiopentone 150 mg, pancuronium 4 mg, 66% nitrous oxide in oxygen and 0.6% ethrane were given. The lungs were ventilated through a 7-mm tracheal tube by a Manley ventilator (tidal volume 400 ml, peak airway pressure 24 cm H_2O) using a fresh gas flow of 4.5 litre min^{-1}. Gentamicin 80 mg and metronidazole 500 mg were given at the request of the surgeon. The patient was put in the lithotomy position with a slight head-down tilt and surgery started, and monitoring (electrocardiograph (CM5 position) and an automatic arterial pressure recorder (Dinamap 845)) was established.

The procedure was uneventful for 40 min. The heart rate was about 120 beat min^{-1} and systolic arterial pressure between 105 and 115 mm Hg. The surgeon had made a longitudinal incision in the lower abdomen and was mobilizing the bowel and bladder, having seen the ventriculo–peritoneal shunt lying free in the abdominal cavity.

The first indication of something untoward was that the heart rate increased to 135 beat min^{-1}, and the arterial pressure decreased to 95 mm Hg.

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This responded initially to infusion of normal saline, but during the next 10 min the heart rate increased gradually to 180 beat min^{-1}, the systolic arterial pressure decreased to 45 mm Hg and the patient became sweaty. The surgeon was informed, the operation abandoned, and resuscitation started. There was good air entry over both sides of the chest, and at this stage she was pink and well perfused peripherally. The inspired oxygen was increased to 100% and 750 ml of normal saline was given rapidly. Despite this the systolic pressure remained at 45 mm Hg, she soon became cyanosed, and her pupils started to dilate. During the next 60 min arterial pressure was supported by injections of ephedrine 3–6 mg (to a total of 45 mg), and intermittently she was given chest compression. The impression was that these measures, particularly the compression, decreased the cyanosis temporarily and certainly decreased the pupillary dilatation. An arterial blood sample, taken during a period of deep cyanosis on 100% oxygen, showed a Pa_{O_2} of 4.1 kPa, a Pa_{CO_2} of 4.5 kPa, with a base excess of -5 mmol $litre^{-1}$. Throughout this period a vigorous heartbeat was palpable and peripheral perfusion was maintained. The cyanosis was not simply a result of low arterial pressure, for there were periods when the patient was cyanosed despite a systolic arterial pressure of greater than 70 mm Hg with a good radial pulse.

Eventually, her colour began to improve and her arterial pressure stabilized. Two hours after the initial incident, she was transferred to the intensive care unit. She had already made ventilatory efforts, and had responded to her name. At that time a definitive diagnosis had not been made, and so neuromuscular function was allowed to return spontaneously. Neostigmine was not given. The trachea was extubated without difficulty and there was by then nothing abnormal on physical examination except for a persistent tachycardia of 130 beat min^{-1}. However, a 12-lead electrocardiogram showed signs of right-heart strain which resolved over the next 6 h. A tentative diagnosis of pulmonary embolism or other cause of acute pulmonary vascular obstruction was made. She breathed oxygen at 4 litre min^{-1} overnight and remained a good colour. We did not take any further arterial samples.

The presumed diagnosis was confirmed the next day by a lung perfusion scan. There was minimal perfusion of the left lung, with some smaller defects of perfusion of the right lung. As there was no significant abnormality on the chest radiograph, the diagnosis was clearly a massive pulmonary embolus.

The patient was transferred from the intensive care unit to the care of the paediatricians, and anticoagulated. Heparin 30000 units per 24 h by infusion gave a satisfactorily prolonged partial thromboplastin time. Warfarin 5 mg was given on the 1st and 2nd days after operation and by the 3rd day her prothrombin ratio was increased such that the heparin could be stopped. There were two small episodes of melaena on the 4th day after operation without any cardiovascular disturbance. As the haemoglobin had decreased from 10.1 g dl^{-1} on the 3rd day after operation to 8.5 g dl^{-1}, two units of blood were transfused. Her only other postoperative problem was a cough productive of clear sputum.

On the 7th day after operation, the patient was discharged home, well in herself, and taking warfarin 3 mg daily. This was later increased by her general practitioner to 4 mg. A repeat lung perfusion scan 7 weeks after the incident was normal.

It was decided to maintain anticoagulation for 6 months in total. No decision has been made yet on the possibility of further surgery.

DISCUSSION

Although thromboembolic phenomena are a common postoperative complication in adults, they are rare in children. Even in adults they have only rarely been diagnosed during the operation, and then there had usually been an understandable aetiology. In two patients the embolism occurred during surgery for resection of abdominal aortic aneurysm (Mangano, 1980; Hecker and Lynch, 1983): one was a patient with polycythaemia (Enright, Quartey and McQueen, 1980) and another was obese, hypertensive and had been immobilized for 1 month before presenting for surgery (Divekar, Kamdar and Pansare, 1981).

We could find no report of true thromboembolism occurring during an operation in a child who had no apparent predisposing or operative cause. There has been a report of embolism, probably of marrow or air, during the insertion of an orthopaedic nail in a child with osteogenesis imperfecta (Fosel et al., 1985) and there are reports of intraoperative tumour embolism in children (Akyon and Arslan, 1981; Dorman, Sumner and Spitz, 1985). Since they are chronically constipated, patients with spina bifida need more rigorous bowel preparation for surgery than do normal patients. Our patient had had some diarrhoea during bowel preparation, but this was not thought to have caused significant dehydration. Clinically, she was perfectly well on the morning of operation, and the induction of anaesthesia had no untoward effect. In any case, Buck's group concluded from their survey of postmortems that dehydration was not by itself a major factor (Buck et al., 1981). Venous thrombosis could occur in a patient immobilized secondary to spina bifida, but this girl was fully mobile. If she had still had a ventriculo-atrial valve *in situ*, that would have been a risk factor, but it had been replaced 3 years earlier by a ventriculo-peritoneal shunt.

There was no family history of unusual thromboembolic phenomena. It may be that she has a biochemical fibrinolytic defect, but investigation of that will have to wait until anticoagulation has been stopped.*

In retrospect, the signs noted during the operation were exactly what one would expect with a massive pulmonary embolus—with the exception, perhaps, that the event was not sudden and catastrophic, but developed over 10 min or so. In view of the patient concerned, it is not surprising that the diagnosis was not made at the time. In one of the adult patients the diagnosis was not made in the operating theatre, but only later when the event recurred on the intensive care unit (Enright, Quartey and McQueen, 1980). Earlier diagnosis would not have altered the outcome. We would still have given a vasopressor, fluid i.v. and cardiac massage; embolectomy was unrealistic.

We have no evidence as to the origin of the embolus. The evolution of the changes in the cardiovascular system could have been the result of more than one embolus, or because the initial changes were caused by a clot in the right ventricle which moved into the pulmonary arteries a few minutes later. Presumably the treatment, particularly the chest compression, then dislodged the clot, mainly into the left lung, and the patient began to improve.

She was profoundly hypoxaemic, far more so than another patient who had a similar systolic arterial pressure (Mangano, 1980). The causes of hypoxaemia after pulmonary embolism are complex. Huet's group concluded that early hypoxaemia is caused by ventilation–perfusion imbalance, rather than by intrapulmonary shunting (Huet et al., 1985). They could not completely rule out the opening of a patent foramen ovale in their patients, and nor can we; but at no time could we hear a cardiac murmur.

"It is clear...that pulmonary embolism, although rare, should be seriously considered when unexplained hypoxia occurs during operation" (Enright, Quartey and McQueen, 1980). We would support that, although it must come at the bottom of a long list in a fit, healthy, mobile child. Nonetheless, "when you have eliminated the impossible, whatever remains, *however improbable*, must be the truth" (Conan Doyle).

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**Note added in proof:* No clotting abnormality was demonstrated. Routine tests were normal, as were protein C, anti-thrombin III, euglobin clot lysis and plasmin activator.

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BOOK REVIEWS

Emergency Anaesthesia. Edited by A. P. Adams, P. B. Hewitt and M. C. Rogers. Published by Edward Arnold, London. Pp. 361 + index; indexed; illustrated.

Professor Adams and his co-editors have gathered together a team of 32 anaesthetists and others from both sides of the Atlantic to produce a pocket-book guide for the handling of anaesthetic procedures. It is aimed particularly at those in training. As such a guide it more than fulfils its aims. The introductory eight chapters cover the principles of emergency anaesthesia and of resuscitation with useful information on i.v. therapy, blood transfusion and the practical procedures needed, together with the basic aspects of monitoring. The subsequent chapters concern the individual systems and their associated emergency problems; two chapters consider the mass casualty problem and those seen in developing countries.

Each chapter begins with a useful contents list and is clearly laid out, ending with a reference list or suggestions for further reading. Were one to attempt to read the book at a sitting, then one might become worried about some repetition from one chapter to the next; however, if the book is read a section at a time, or as a true pocket guide to help with an unexpected emergency, this problem does not arise. Perhaps there is some overkill with the chapters on, say, renal failure and major vascular surgery, where the emphasis is on the handling of any patient with renal failure or in need of a vascular operation—the emergency aspects are less well handled. Nevertheless, the book as a whole is a good, comprehensive guide to current clinical practice and will join those bench books which should be available wherever emergency anaesthesia is practised.

J. Norman

Liver Failure. Edited by R. Williams. Published by Churchill Livingstone. Pp. 230; indexed; illustrated.

Liver Failure is the most recent addition to the series, *Clinics in Critical Care Medicine*. Eighteen international experts contribute 12 chapters on the most important current aspects of liver failure, and discuss their clinical findings and research areas.

The Editor, in his introduction, discusses the great importance of distinguishing between fulminant hepatic failure with a previously normal liver and acute decompensation in patients with chronic liver disease. Possible mechanisms for mediation of hepatic encephalopathy are discussed followed by cerebral oedema, cardiovascular, pulmonary and renal disturbances in liver failure. Whilst paracetamol overdose and viral hepatitis are still the major causes of fulminant hepatic failure, repeated halothane anaesthesia is a rare cause. A whole chapter is devoted to specific therapy for paracetamol overdose.

Infective complications, variceal haemorrhage and coagulation patterns in chronic liver disease are discussed, together with practical aspects of their management. There is a review of the extensive and controversial literature on the use of amino acids in hepatic failure. Despite the need for further work to evaluate the role of branched-chain amino acids before definite recommendations can be made, this chapter is a model of clarity.

The results of artificial liver support from Montreal and Kings College Hospital are detailed. Artificial cells have been developed which retain "immobilized enzymes" without producing an immunological reaction. These have been used in animal studies.

This book is ideal for the general intensive care practitioner who sees liver failure rather infrequently. It clarifies pathophysiology, evaluates alternative therapies and stresses always the importance of objectivity. Scoring systems for coagulation abnormalities, degree of liver failure and outcome after porto-caval shunting enable a true comparison of alternative therapies.

There are minor criticisms. The section on haemodynamic changes during charcoal haemoperfusion would benefit from further explanation of derived variables, and a chapter devoted to hepatic transplantation would be invaluable for anaesthetists. The book would benefit by some concluding comments and indication of future evolution of management.

Nevertheless, this is an excellent text which I would unreservedly recommend to all anaesthetists and intensive therapy practitioners.

S. M. Willatts

Pulse Oximetry. Edited by J. P. Payne and J. W. Severinghaus. Published by Springer-Verlag. Pp. 193 plus index; indexed; illustrated. Price £29.

Hypoxaemia is the major cause of anaesthetic-related deaths. Because pulse oximetry is a rapid, continuous and non-invasive technique, it is set to revolutionize monitoring of patients during anaesthesia and intensive care for, as Dr John Nunn says, "our starting point must be to recognise how very unsatisfactory are the unaided human senses in monitoring oxygen". *Pulse Oximetry* is the proceedings of a Symposium held in Britain in 1985. This was the third meeting in the past 21 years concerned with oxygen measurements sponsored by the Health Care Division of the British Oxygen Company and held under the auspices of the Research Department of Anaesthetics of the Royal College of Surgeons of England.

This book makes interesting reading and starts with the history of monitoring oxygenation by John Severinghaus, followed by an account of pulse oximetry and oxygen transport. The editors have sensibly added a section on definitions and symbols, because different methods of determining the amount of saturation of haemoglobin with oxygen can produce different answers. If we could adjust our minds it might be better to read the display in terms of desaturation rather than saturation. We are certainly going to have to do that in terms of thinking again about saturation, as tension has predominantly occupied our thinking over the past 20 years or so. Pulse oximetry—at two wavelengths—cannot distinguish between forms of haemoglobin such as methaemoglobin, sulphaemoglobin and carboxyhaemoglobin; there seems to be disagreement regarding possible interference from increased bilirubin concentrations. The following chapters discuss the interrelation of oxygen tension, oxyhaemoglobin saturation and oxygen content and the rest of the book is given over to accounts of the advantages or uses of pulse oximetry in almost every conceivable situation, including diving. There are one or two voices of dissent, such as Professor Andrew Thornton's conclusion that ear-lobe oximetry is not recommended for routine monitoring of dental patients undergoing general anaesthesia or sedation. However, pulse oximetry was not available to him at the time he performed his studies and he does say unequivocally that continuous monitoring of oxygen saturation has been a useful method for highlighting deficiencies of technique in dental anaesthesia.

A feature of this book is the excellent discussion sections, which are interposed between groups of chapters. Here can be found the voice of sound common sense in Dr Ross Holland from New South Wales, who states that it is absolute garbage to assume that the only reason why things go wrong under anaesthesia and why people die, for example, is because of a mishap. He points out that, whereas this is true in 20% of patients (e.g. disconnection, misplaced tracheal tube, compromised airway), the other 80% who die in association with anaesthesia do so because somebody gave the wrong anaesthetic at the wrong time or they made an error of judgement and all the monitoring in the world would not have made any difference (e.g. inhalation of vomit). He emphasizes there is only one absolutely indispensable monitor and that is a trained, experienced person in the operating room.

Let us hope that basic lessons from this work, such as those demonstrated by Drs Hanning and Abbott who detail the hypoxaemia that often occurs in the early stages of recovery from anaesthesia—that is during transportation from the operating theatre to the recovery room, and in the recovery room itself—will get home to anaesthetists.

The major criticism of this work is that it appears to promote the sponsor's product the Biox oximeter. This is unfortunate as, given the title, the reader would have been greatly helped by an unbiased informed account of the merits and demerits (including differences in technology) of the other pulse oximeters which are available (e.g. Nellcor, Novametrix). Questions on the technology and performance of competitor's oximeters have largely gone unanswered.

A. P. Adams

600 MCQs in Anaesthesia: Clinical Practice. By P. J. Simpson and N. W. Goodman. Published by: Churchill Livingstone, Edinburgh. Pp. 232; not indexed or illustrated.

Simpson and Goodman have previously produced a set of MCQ papers for the basic science of anaesthesia. This compilation of 10 papers with 60 questions in each follows the same model, but is directed at clinical practice—in essence, at the Parts I and III of the F.F.A.R.C.S. The introduction offers the usual, necessary advice for all taking such examinations, in terms of handling MCQ papers. The papers are a good mix and any candidate using them as a practice will get a reasonable assessment of his or her likely mark.

The problem that candidates will have in using these sets will be in trying to make a distinction between the knowledge required for the Part I and that for the Part III examination. Each paper contains some questions on special anaesthesia which will be more appropriate for the advanced trainee.

The main use of the book will thus be to enable candidates to assess their level of knowledge, especially if it is used as a mock examination. One can also then learn from one's mistakes. It would be a mistake to use the book as a prime source of knowledge; that should come from good teaching, clinical experience and the use of other printed materials. The other use for the book will be for trainers—to assess their level of knowledge!

J. Norman

Handbook of Local Anesthesia. By Stanley F. Malamed. Published by the C. V. Mosby Company. Pp. 297; indexed; illustrated.

This book is about local anaesthesia for dentistry. It is clearly the work of a great enthusiast who has gone to great lengths to produce a meticulously detailed and wide-ranging work that makes interesting reading whether you are a dentist or an anaesthetist.

It starts by covering the neurophysiology of nerve conduction and the general principles of the pharmacology of local anaesthetic agents. The author discusses each of the commonly-used local anaesthetics in detail, and the vasoconstrictors. The next section on the armamentarium deals with equipment, syringes, needles, cartridges and so on, their use and care.

The largest section of the book covers the techniques and is well illustrated with drawings and photographs. It starts by dealing with the medical assessment of patients and has a sensible discussion about common medical conditions and how these interact with dental treatment and local anaesthesia. My only major criticism of this book occurs in this area. The author states that amide-type local anaesthetics are absolutely contraindicated for malignant hyperpyrexia susceptible patients. He recommends ester-type local anaesthetics for such patients. This statement is erroneous and could lead to serious problems. There is no evidence that MHS patients are at risk from amide local anaesthetics and by recommending esters, which can cause serious allergy, these patients are being subjected to an unnecessary risk. This section goes on to discuss the general care of patients in the dental surgery and then covers the anatomy of the trigeminal nerve, the maxilla and the mandible. The two chapters on maxillary and mandibular anaesthesia cover many different blocks in great detail, with excellent illustrations. The final chapter in this section covers the application of local anaesthesia to the various dental specialties, including a useful section on paediatric dentistry.

The final section of the book deals with complications, both local and systemic, and their management. The section on treatment of systemic toxicity is clear and lays the emphasis on keeping the patient oxygenated, although no mention is made of tracheal intubation, despite the fact that, in the section on laryngeal oedema resulting from allergy, cricothyrotomy is described.

I found this an interesting and well produced book which covers its subject in sufficient detail to give its readers a thorough understanding of local anaesthesia for dentistry. I hope my own dentist has read it!

W. Macrae

A Pocket-Book for Intensive Care. By J. Tinker and S. N. Jones. Published by Edward Arnold (Publishers) Ltd, London. Pp. 143; indexed; illustrated. Price £7.25.

This short work seeks to provide "useful practical information for medical and nursing staff working in intensive care units." The authors point out that it is not an addition to the range of works offering detailed instructions on clinical management.

The subject matter is laid out in eight chapters on different systemic topics and the book contains much useful information.

The book also acts as an eloquent testimony to many of the confusions of current intensive care practice—for example, approximately 5% of the book is given over to tables of infusion regimens for drugs, setting out at great length infusion rates in drops/min, for a wide variety of infusion sets, all of which seems only to underline the confusion occasioned by the use of such prescriptions in the first place, when devices for delivering volumes directly are available. Another area of confusion which the book highlights is in the use of units. The normal values for various biochemical measurements are given correctly in molar units. However, for the majority of drugs the therapeutic concentrations are routinely given only in microgram and milligram units, with the concentrations of very few drugs being given in the molar units which seem to be preferred by biochemistry laboratories. Overall, however, the book is a useful compendium of practical data, despite numerous irritating omissions.

In the chapter on infection, for example, there is a table of antibiotics with guidance as to the use and recommended doses; for a number of these antibiotics the book correctly instructs one to monitor plasma concentrations. Unfortunately, nowhere in the book does it give any guidance as to what plasma concentrations might be found to be acceptable, and this example highlights my principal criticism of the work as a whole. While the authors have chosen to emphasize the practical rather than the overall view of clinical management, one must really question that judgement. Clinical practice is a permanent tension between thinking and doing, and Intensive Carè has perhaps in the past suffered from an excess of the latter at the expense of the former. This reviewer is concerned that the book does nothing to redress that imbalance of attitude. The book in the end leaves one with the taste of dry bread in the mouth, when what one really wanted was a nourishing sandwich and at the price proposed the work could not be preferred to some of the more comprehensive volumes available, for example—the *Oxford Handbook of Clinical Medicine*. Indeed, one might go so far as to say that if the blank pages in the latter were used to contain some of the information available in the current work, then the perfect pocket book would be available.

W. G. Anderson

Current European Anaesthesiology—The Yearbook of the European Academy of Anaesthesiologists—Vol. 2, 1986. Edited by R. M. Jones. Published by John Wiley and Sons. Pp. 308; indexed. Price £29.50.

This book reviews 168 articles from 18 European journals. Comments on each article are provided by one of 79 reviewers from Europe (with two North American exceptions) under 10 sectional headings. The articles are intelligently juxtapositioned, and current interests are reflected in the frequency of articles appearing in each section (e.g. the use of propofol, and anaphylactoid reactions in the pharmacology section; post-operative analgesia and day case anaesthesia in the section on clinical practice). However, the wisdom of including articles which are themselves a review may sometimes be questioned, losing the opportunity of appraisal of original investigations by the mostly excellent reviewers.

Articles relating to recurring interests are present (tracheal cuff volumes and pressures, evaluation of automatic oscillometers, failed intubation in obstetrics); as well as recently introduced themes (the development of the use of extradural opioids). Additionally, topics of general interest with novel developments are featured (anaesthetic knowledge among surgeons; the *in vitro* buffering capacity of Alka Seltzer).

There are a number of extracting journals and books published relating to anaesthetic literature; it may be asked, therefore, is this a necessary addition? For which sector of the anaesthetic community is this book intended? For the reader who is interested in the details of particular aspects of a specialty, the summaries of the articles featured may appear too short, while for the browser who delves at random into the book, some may appear too long. However, the opinions of the reviewers, although containing in certain places their sometimes biased views, provide thoughtful comment for both the clinician and researcher, as well as for the occasional reader. Certainly, there is much variety here, and in this respect the book achieves its stated aim—to provide a broad view of current research and practice.

To compile such an erudite and eclectic work must be a demanding task, and the editors are to be congratulated. The salutary aphorism of Proust placed in the front of the book reminds us of the potentially transient nature of our assertions on our subject, which provides the motivation to produce a book of this kind.

D. Fell

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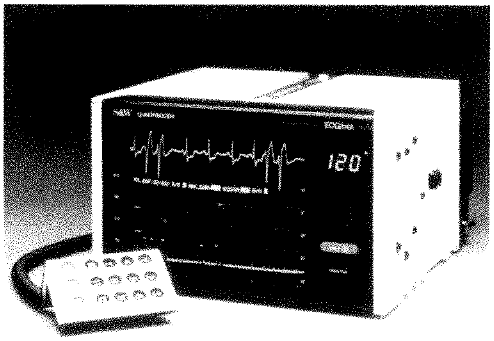

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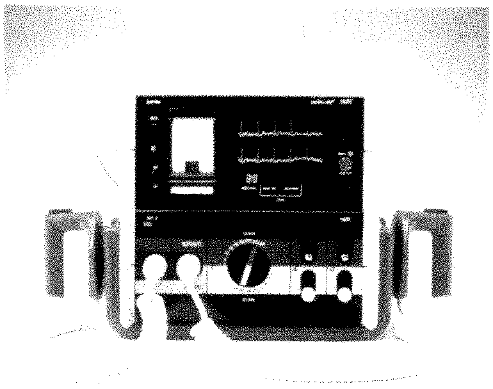

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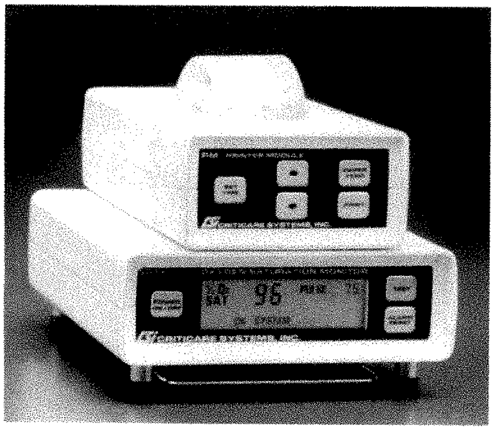

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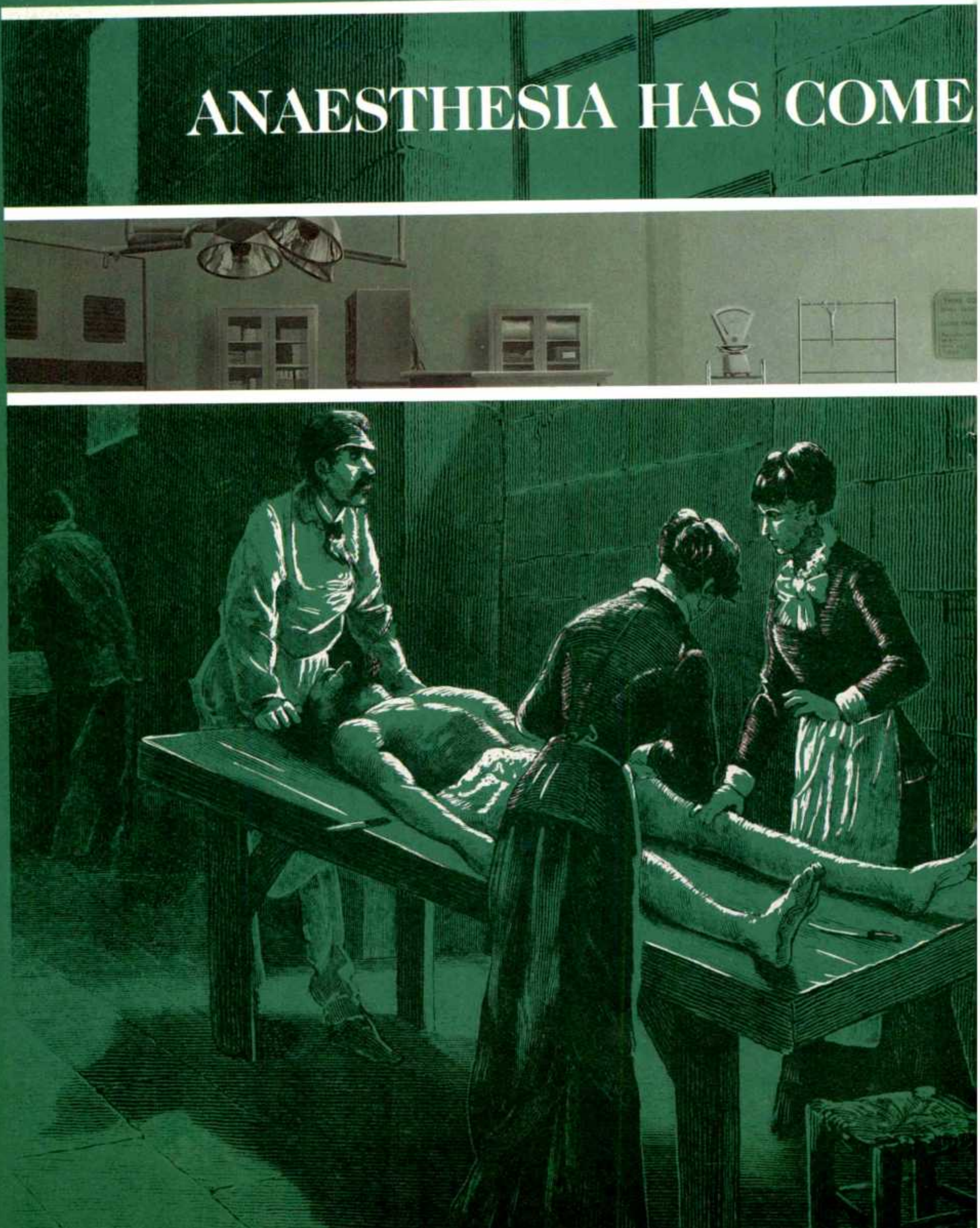

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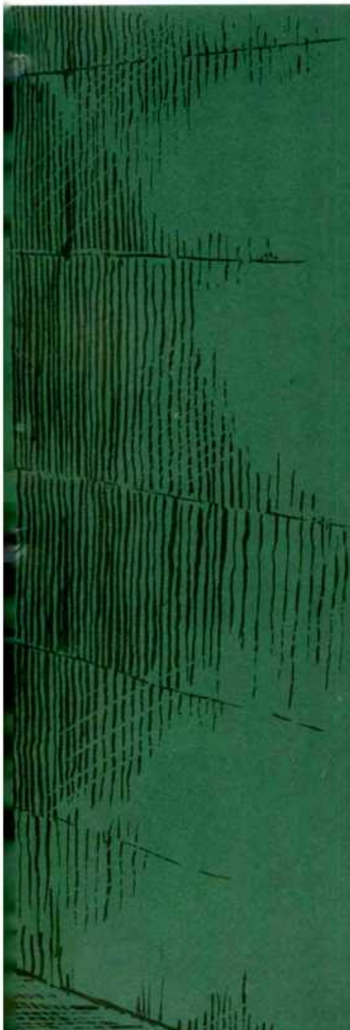

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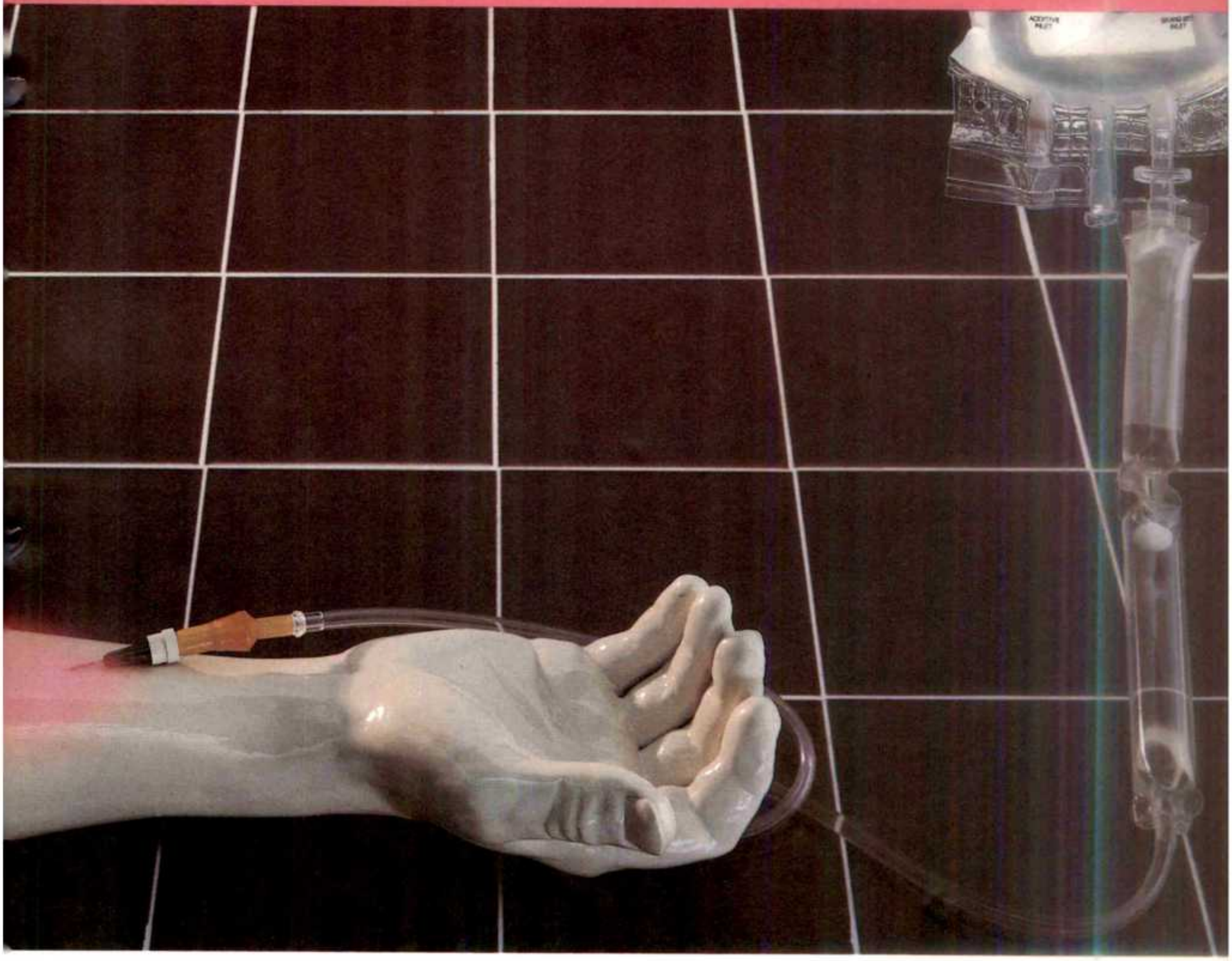

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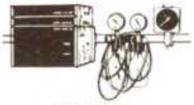
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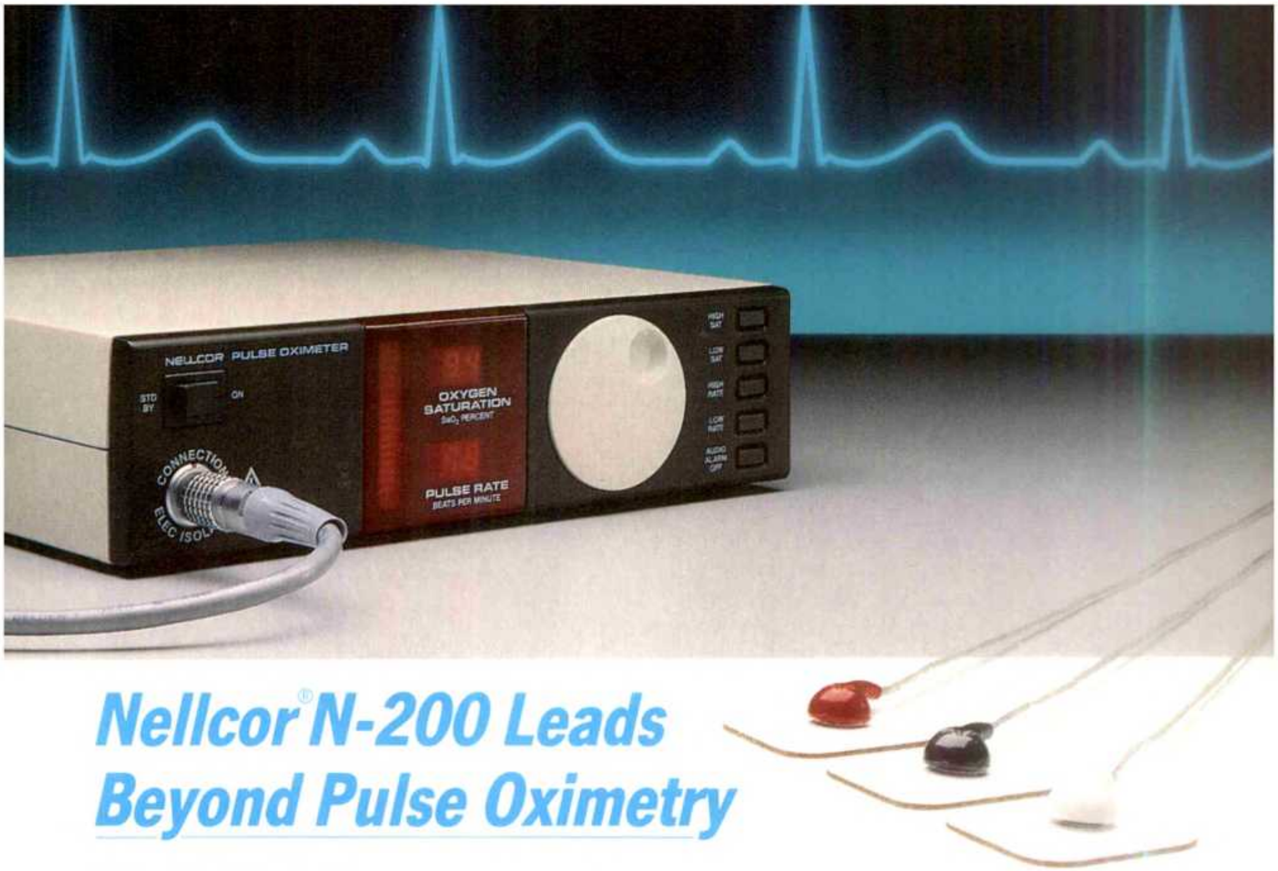

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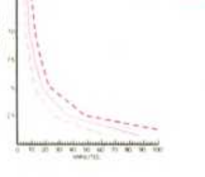

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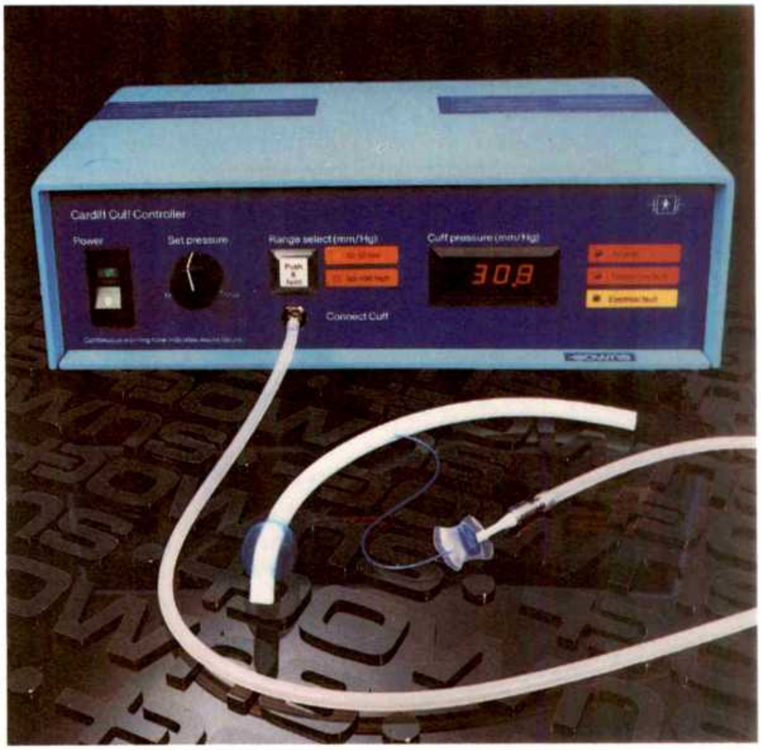

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The following changes should be noted with immediate effect:

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Editor, British Journal of Anaesthesia
University Department of Anaesthesia
Leicester Royal Infirmary
Leicester LE1 5WW.

The system of references to be used in *British Journal of Anaesthesia* has been changed from Harvard to Vancouver style. Full information on the system to be used is provided in the current Guide to Contributors (pp. viii, x, xii of each issue) and all new material submitted must follow this format.

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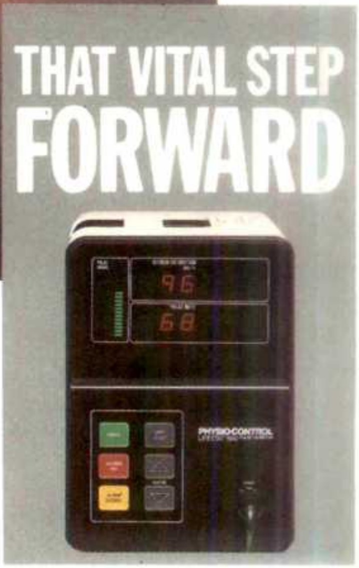

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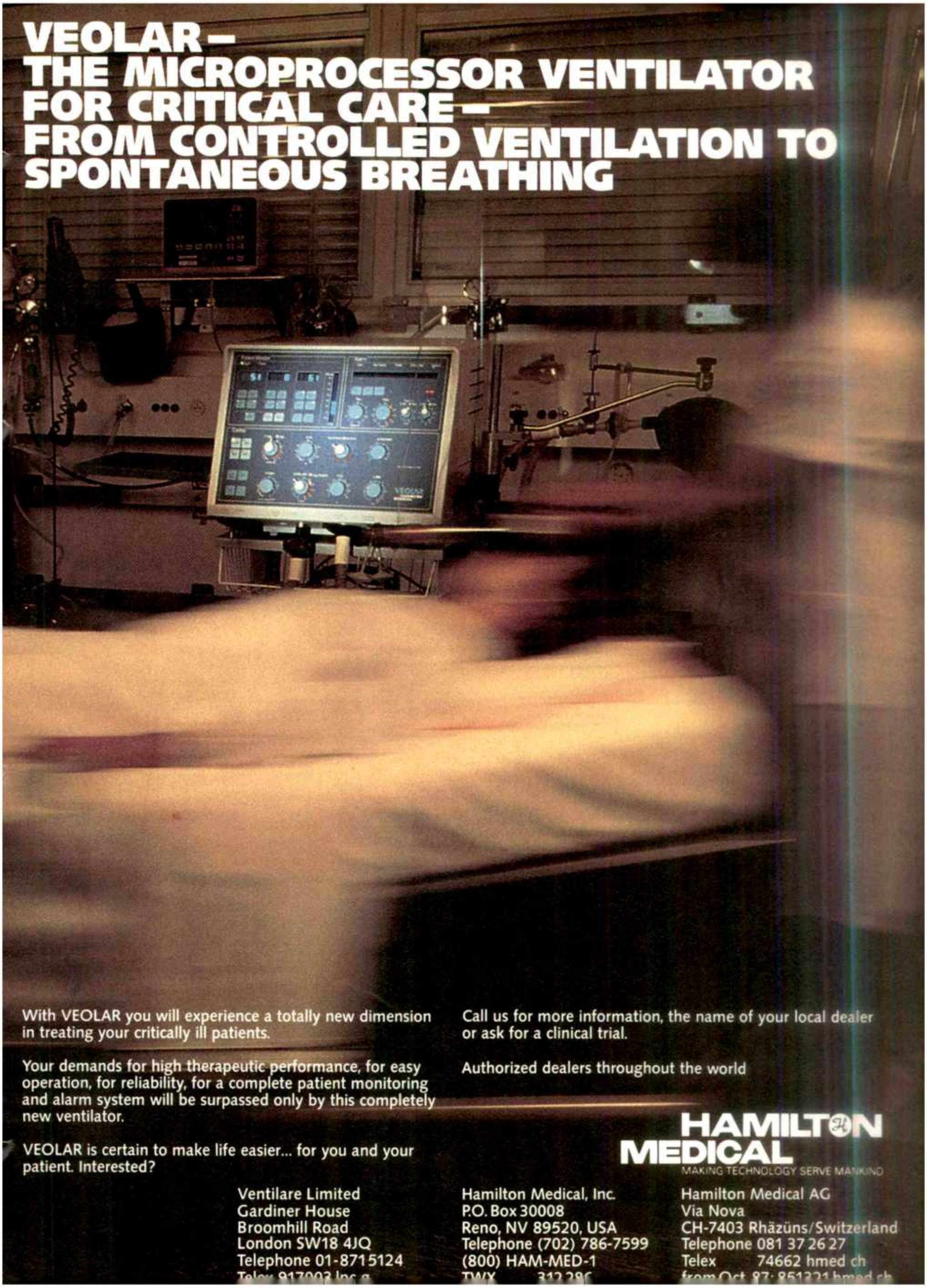

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BRITISH JOURNAL OF ANAESTHESIA

VOLUME 59, No. 9 SEPTEMBER 1987

EDITORIAL

A BRITISH FOOTNOTE TO THE LIFE OF HORACE WELLS

The most tragic story in the history of anaesthesia is that of Horace Wells, the dentist who practised in Hartford, Connecticut, U.S.A. in the middle of the last century and who was the first to use nitrous oxide anaesthesia. The Hartford Museum of Historical Medicine and Dentistry has a collection of items associated with Wells, which includes his practice day book, passport and a number of pictures. Among the collection is a certificate (fig. 1) of previously unknown provenance, to which there is no reference in any modern work. This Editorial outlines the story behind it.

At an exhibition of the effects of nitrous oxide given in Hartford by Gardiner Colton on December 11, 1844, Wells conceived the idea of inhaling the gas to produce insensibility during dental extractions. On the next day, according to the account of his colleague, Joseph Riggs, Wells sat in his own dental chair with a bag of nitrous oxide (provided by Colton) in his lap. When insensibility overtook Wells, Riggs extracted a molar tooth. Wells used nitrous oxide successfully on other occasions and then travelled to Boston to demonstrate its effects before a class at the Harvard Medical School. At the time the demonstration was considered to be a fiasco and Wells returned to Hartford a disappointed, if not a broken, man. From then on he practised dentistry sporadically, as is obvious from his own records and the advertisements that he placed in the local newspapers (Menczer, Mittleman and Wildsmith, 1985). This extreme reaction would seem to have been the first outward sign of a major depressive illness.

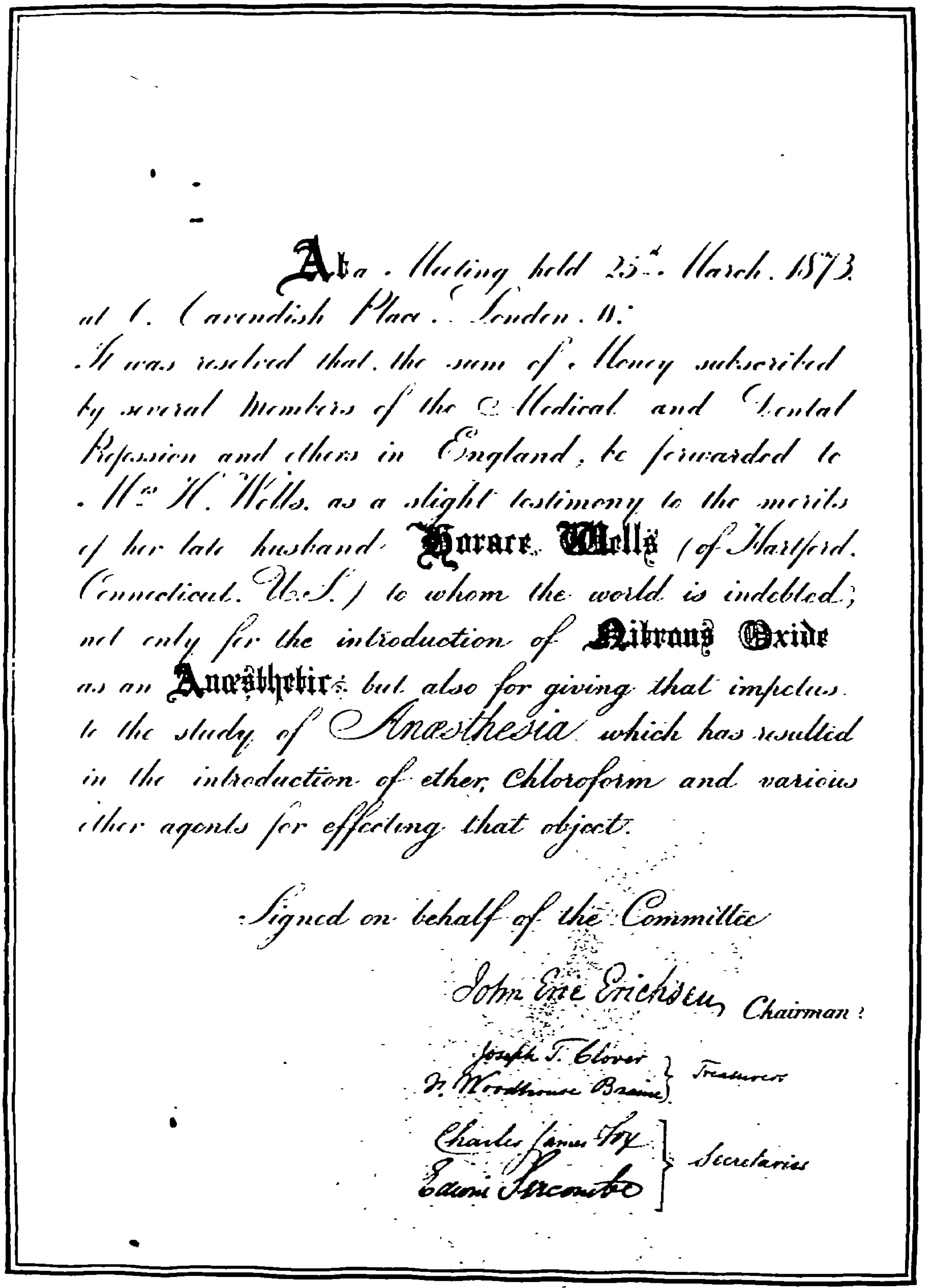
Nearly 2 years later, William Morton gave his definitive demonstration of the effects of inhaling ether. Morton (a former student and partner of Wells) had been present at the abortive attempt to demonstrate nitrous oxide, but gave Wells no credit, not even for introducing him to the concept of anaesthetic inhalation. Wells, his depression worsened by Morton's success, became obsessed with proving his role in the discovery of anaesthesia. He published his own account (Wells, 1847) of the early history of anaesthesia, and travelled to Paris to present his claim for priority to the French Royal Academy of Medicine (Smith, 1966a), arguably the most important medical forum in the world at that time.

Later in 1847, Wells returned to Hartford and then moved to New York. Little is known of his short time there until, claiming to have been under the influence of chloroform, he was arrested on January 21, 1848 on a charge of throwing vitriol into a woman's face. While in prison he committed suicide by cutting his femoral artery, the letters he wrote before this act indicating just how tortured his mind had become. For example:

> "My brain is on fire.... Before 12 o'clock this night I am to pay the debt of nature. Yes, if I was to go free tomorrow, I could not live and be called a villain. God knows I am not one."

The news sent by C. S. Brewster, an American dentist practising in Paris, that his principal role in the discovery of anaesthesia had been acknowledged in France arrived after Wells' death—too late to save him.

Colton continued with his demonstrations and included reference to Wells in his presentations, but few if any nitrous oxide anaesthetics were given between the latter's death and 1862. In that year in New Britain, Connecticut a patient who had heard Colton lecture asked if he would give her the gas, rather than ether or chloroform of which she was afraid, for an extraction. This was done and the local dentists were so impressed that they began to use nitrous oxide regularly (Sims, 1873) because it was clearly superior to the available volatile agents for brief dental procedures. Its use grew rapidly (Smith, 1966b). Colton himself moved to New York, formed the Colton Dental Association and by 1871 claimed to have used nitrous oxide in more than 51000



At a Meeting held 25th March 1873
at 6 Cavendish Place London W.
It was resolved that the sum of Money subscribed
by several Members of the Medical and Dental
Profession and others in England, be forwarded to
Mrs H. Wells, as a slight testimony to the merits
of her late husband **Horace Wells** (of Hartford,
Connecticut. U.S.) to whom the world is indebted;
not only for the introduction of **Nitrous Oxide**
as an **Anæsthetic**, but also for giving that impetus
to the study of Anæsthesia which has resulted
in the introduction of ether, Chloroform and various
other agents for effecting that object.

Signed on behalf of the Committee

John Eric Erichsen Chairman:

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FIG. 1. The certificate sent to Mrs Wells.

At a Meeting held 25th March 1873 at 6 Cavendish Place, London W:

It was resolved that the sum of Money subscribed by several Members of the Medical and Dental Profession and others in England, be forwarded to Mrs H. Wells, as slight testimony to the merits of her late husband **Horace Wells** (of Hartford, Connecticut, U.S.) to whom the world is indebted, not only for the introduction of **Nitrous Oxide** as an **Anaesthetic** but also for giving that impetus to the study of Anaesthesia which has resulted in the introduction of ether, chloroform and various other agents for effecting that object.

Signed on behalf of the Committee

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patients (Fox, 1871). Nitrous oxide was introduced to Britain in 1868 by Thomas Evans, another American dentist who worked with Brewster in Paris (Smith, 1966c).

Colton visited London in 1868 and again in 1871. He was always scrupulous about awarding full credit for the discovery to Wells, and indicated that his widow and son had not been adequately provided for after Wells' early death. Charles James Fox, a leading London dental surgeon who had been an early enthusiast for nitrous oxide, conceived the idea of raising a public subscription on their behalf (Fox, 1871). A joint medical and dental committee was formed with the aim of raising funds from the public as well as from the two professions. John Erichsen, an eminent surgeon, was the chairman, Edwin Sercombe shared the duties of secretary with Fox, the treasurers were Joseph Clover and Woodhouse Braine and many other members of both professions lent their names in support.

Between 1871 and 1873 the *British Journal of Dental Science* gave the issue a great deal of attention, but the minimal space given to it in other journals seems to have matched the overall response of both the public and the two professions, for the sums raised were miserly. Not every member of the "committee" was among the list of subscribers, fewer than 200 of whom contributed a total of £149. In comparison, during approximately the same period of time, the dental profession alone contributed over £2000 towards the cost of the new London Dental Hospital. The sum of money collected (£149) was forwarded to Mrs Wells with the certificate (fig. 1), inscribed on vellum and signed by the five office bearers of the committee. The certificate was found a few years ago in a box containing other items associated with Wells. There is no record of how it came into the possession of the Hartford Museum of Historical Medicine and Dentistry, where it is now on display in the "Wells" room.

J. A. W. Wildsmith
L. F. Menczer

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Br. J. Anaesth. (1987), 59, 1070–1079

COMPARISON OF THE RESPIRATORY DEPRESSANT EFFECTS OF HALOTHANE AND ISOFLURANE IN ROUTINE SURGERY

K. ALAGESAN, J. F. NUNN, T. W. FEELEY AND C. P. H. HENEGHAN

SUMMARY

Respiratory depression has been studied in 21 patients anaesthetized with either halothane and nitrous oxide, or isoflurane and nitrous oxide while undergoing routine surgery. Spontaneous ventilation was preserved and the end-tidal concentrations of the two volatile anaesthetics were at approximately equal MAC-multiples. The minute volume of pulmonary ventilation was not significantly different for the two anaesthetics, but tidal volume was significantly greater and frequency significantly lower with isoflurane. Arterial and end-tidal P_{CO_2} *were consistently lower in the patients receiving isoflurane, the difference being significant in many of the sub-groups. There was no evidence of a progressive increase in* P_{CO_2} *with either anaesthetic during surgery lasting up to 225 min. Mean values for* P_{CO_2}*, however, tended to be well above the normal reference range, with mean arterial* P_{CO_2} *in the range 7.2–8.6 kPa.*

Fourcade and colleagues demonstrated (1971) that isoflurane caused a severe dose-related depression of ventilation in unpremedicated volunteers not undergoing surgery, and that this was greater than for other volatile anaesthetics given under comparable circumstances (Eger, 1981). However, it is difficult to extrapolate from these laboratory studies to the clinical situation in which opioid premedication and the administration of thiopentone can be expected to cause additional respiratory depression. Conversely, it has been shown that surgery can partially reverse the respiratory depressant effects of either isoflurane or halothane (Eger et al., 1972; France et al., 1974). Furthermore, the use of nitrous oxide reduces the concentration of volatile agent which is required and so tends to cause less respiratory depression for the same depth of anaesthesia. In addition to the effect of these factors, we lack information on changes in $P\text{co}_2$ during the course of a long operation when isoflurane is used with preserved spontaneous ventilation. With so many variables and uncertainties, it is not clear whether isoflurane is, in fact, less suitable than halothane or even whether it is contraindicated for use during anaesthesia under these circumstances.

We have, therefore, compared the respiratory effects of halothane and isoflurane during varicose vein and orthopaedic surgery in patients breathing spontaneously while adhering to conventional routine anaesthetic practice in all material respects. In our first series of patients, the end-tidal concentrations of the volatile anaesthetics were monitored with a mass spectrometer and inspired concentrations of the two volatile anaesthetics were adjusted to give similar multiples of the minimal alveolar concentration (MAC) required for anaesthesia (Stevens et al., 1975). In our second series, the anaesthetist chose the inspired concentration of the volatile anaesthetic agent on purely clinical grounds, being unaware of the end-tidal concentration. In a third series we observed changes during more prolonged anaesthesia.

K. ALAGESAN,* M.B., B.S., F.F.A.R.C.S.; J. F. NUNN, M.D., PH.D., F.R.C.S., F.F.A.R.C.S., F.F.A.R.A.C.S.(HON.), F.F.A.R.C.S.I.(HON.); T. W. FEELEY,† M.D.; C. P. H. HENEGHAN, B.A., B.M., B.CH., F.F.A.R.C.S.; Division of Anaesthesia, Clinical Research Centre (and *Department of Anaesthetics), Northwick Park Hospital, Watford Road, Harrow, Middlesex HA1 3UJ. Accepted for Publication: March 5, 1987.

Present addresses:

*Department of Anaesthetics, Lincoln County Hospital, Sewell Road, Lincoln.

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PATIENTS AND METHODS

Patients in series A and B were scheduled for varicose vein surgery and belonged to ASA groups I or II. Informed consent was obtained for the study, which was approved by the hospital ethics committee. Clinical care and routine monitoring of the patient were the responsibility of an independent anaesthetist who was not directly involved in making any special measurements. The means and ranges of the duration of surgery, age and weight of the patients are given in table I. All patients received papaveretum 0.30 mg kg^{-1} and hyoscine 6.0 μg kg^{-1} i.m. approximately 1 h before the induction of anaesthesia. Patients were randomly allocated to receive either isoflurane or halothane.

On arrival at the induction room a cannula was placed in a suitable vein and the patients were pre-curarized with pancuronium 0.75 mg and pre-oxygenated for 5 min. Anaesthesia was induced with thiopentone 3.5 mg kg^{-1}, and a tracheal tube was inserted following the administration of suxamethonium 1.5 mg kg^{-1}. Ventilation was assisted manually, using a Magill breathing system, with a mixture of 70% nitrous oxide in oxygen until spontaneous breathing resumed. The breathing system was then changed to a valvular non-rebreathing system previously described (Alagesan and Nunn, 1986), to exclude the possibility of rebreathing. Administration of the volatile anaesthetic agent was started and continued for a mean time of 20 min before the start of surgery.

End-tidal carbon dioxide concentration was measured with a Hewlett–Packard capnometer (model 47210A) with it's "breathe-through" cell connected between the catheter mount of the tracheal tube and the breathing system. The capnometer was calibrated using the carbon dioxide cell provided by the manufacturers, which we had verified against a standard mixture of 10% carbon dioxide and 90% nitrogen. The inspired concentration of the volatile anaesthetic agent was measured with an Engstrom Emma Multigas analyser, sampling dry from the inspiratory limb of the circuit. It was calibrated before and after each patient with a standard gas mixture prepared by pressure dilution, and verified with gas chromatography against a volumetric standard. Tidal volume was measured with a Wright's respirometer in series with the breathing circuit and ventilatory rate counted with a stop-watch. The response of the Wright respirometer is close to 100% for a patient breathing nitrous oxide at a minute volume of 4.5–5 litre min^{-1} (Nunn and Ezi-Ashi, 1962).

Series A

In this series of 12 patients, end-tidal and inspired anaesthetic vapour concentrations were measured with a mass spectrometer (Medishield Multigas Monitor MS2) tuned to the volatile inhalation anaesthetic agent in use, with its probe inserted to the connector of the catheter mount close to the tracheal tube. Calibration was as described for the Emma above. The inspired concentrations were continuously adjusted to maintain equivalent MAC-multiples in the end-tidal gas for each of the two volatile agents (0.55% halothane and 0.88% isoflurane) (table II). In the presence of 70% nitrous oxide in oxygen, this was intended to give a total MAC of about 1.4 in each group. Assumed MAC values were 0.75% for halothane (Saidman and Eger, 1964), 1.15% for isoflurane (Stevens et al., 1975) and 104% for nitrous oxide (Hornbein et al., 1982). Alveolar nitrous oxide concentration was assumed equal to the inspired concentration which was determined from the rotameters.

Arterial blood samples were taken by radial artery puncture at roughly 10 and 30 min after the start of surgery and analysed immediately for

TABLE I. *Details of patients*

	Volatile anaesthetic	No. patients		Duration of surgery (min)		Weight (kg)		Age (yr)	
		M	F	Mean	SD	Mean	Range	Mean	Range
Series A	Halothane	0	6	45	15.2	60.2	46–75	44.2	35–63
	Isoflurane	3	3	41.7	13.3	73.7	61–94	48.5	29–64
Series B	Halothane	2	5	47.9	13.8	66.2	54–75	49.4	37–58
	Isoflurane	3	5	36.3	15.3	66.7	56–76	35.4	26–41
Series C	Isoflurane	3	2	210	27.7	67.0	55–70	61.0	28–80

TABLE II. *Inspired and end-tidal concentrations of anaesthetics*

		Inspired concentration				End-tidal concentration				Estimated MAC values		
		%		Regression against duration of surgery		%		Regression against duration of surgery				
	Volatile anaesthetic	Mean	SD	r	P	Mean	SD	r	P	Volatile anaesthetic	Nitrous oxide	Total
Series A	Halothane	1.20	0.09	−0.66	0.05	0.55	0.03	−0.56	ns	0.73	0.66	1.39
	Isoflurane	1.40	0.07	−0.43	ns	0.88	0.05	+0.53	ns	0.77	0.66	1.43
Series B	Halothane	1.79	0.12	−0.21	ns	0.82 (derived)		—	—	1.09	0.66	1.75
	Isoflurane	2.00	0.20	−0.86	< 0.01	1.26 (derived)		—	—	1.10	0.66	1.76
Series C	Isoflurane	1.57	0.09	−0.73	< 0.01	0.99 (derived)		—	—	0.86	0.66	1.52

Pa_{CO_2}, Pa_{O_2} and pH using an Instrumentation Laboratory System 1302.

Series B

In this series of 15 patients, the methodology was identical to that described above, except that the mass spectrometer was not used and the anaesthetist was aware only of the inspired concentrations measured with the Emma analyser. He followed normal clinical practice by adjusting the inspired concentrations of halothane or isoflurane (table II) according to the required depth of anaesthesia as judged on clinical grounds. Arterial samples were taken as described for series A.

Series C

This series was designed to look at more prolonged anaesthesia. It comprised five patients undergoing orthopaedic surgery (table I), whose operations lasted between 65 and 225 min. Clinical management was as described for series B, but all received isoflurane. We measured only inspired isoflurane concentration (with the Engstrom Emma Multigas analyser) and end-tidal $P\text{CO}_2$ as described above. Ventilation was not measured in this series and arterial samples were not taken. Since there was no imposed choice of anaesthetic or invasive monitoring, the age range was extended to 80 yr and no permission was deemed necessary. The anaesthetist in charge of the patient remained unaware of end-tidal $P\text{CO}_2$ or of the concentration of anaesthetic. Atropine 0.6 mg was substituted for hyoscine in patients older than 60 yr.

Statistical methods

Means of groups were compared by Student's *t* test except when distribution was not normal, in which cases we used the Mann–Whitney test. Linear regression analysis was applied to assess any trend with time.

RESULTS

Concentrations of anaesthetic agent

In series A, the measured mean end-tidal concentration of halothane was 0.55 (SD 0.03) % and isoflurane 0.88 (SD 0.05) %, corresponding to MAC values of 0.73 and 0.77, respectively (table II). There were no significant trends with time for end-tidal concentrations of either halothane or isoflurane. The target end-tidal values were achieved during surgery with mean inspired concentrations of 1.2% halothane and 1.4% isoflurane. There was a significant reduction of inspired concentration with time for halothane but not isoflurane. The mean end-tidal concentration of the vapour as a percentage of the inspired concentration, from 5 to 40 min after the start of surgery, was 50.4% for halothane and 57.6% for isoflurane (fig. 1), the difference being significant ($P < 0.001$). Neither ratio showed any significant trend with time.

In series B, the anaesthetist responsible for the patients selected a mean inspired halothane concentration of 1.79% and there was no significant trend during a mean duration of 50 min (table II). The corresponding mean inspired concentration of isoflurane was 2.00%,

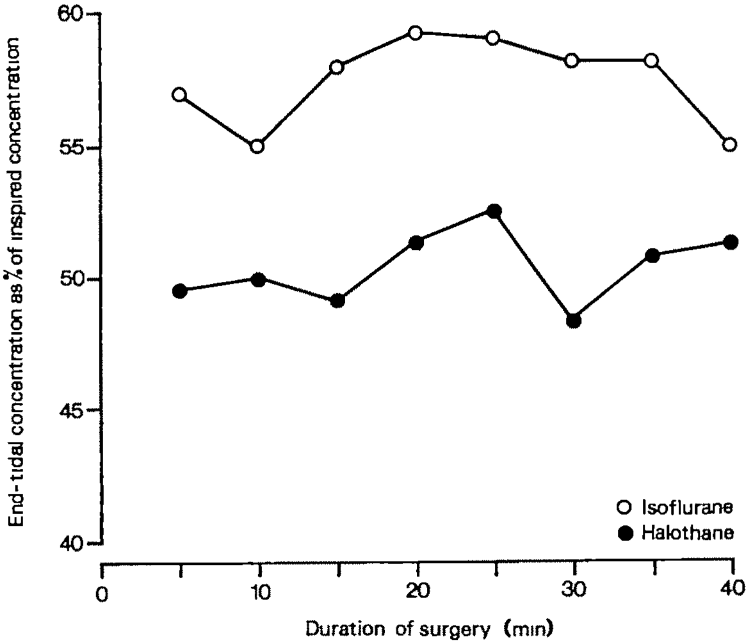

FIG. 1. End-tidal concentrations of the volatile anaesthetics as a percentage of simultaneous inspired concentration, plotted against duration of surgery.

but there was a significant decrease during surgery. Mean end-tidal halothane and isoflurane concentrations were estimated indirectly from the mean inspired values using the ratio of the mean end-tidal concentration to the mean inspired concentration measured in series A, and derived values were 0.82% for halothane and 1.26% for isoflurane, the corresponding MAC-multiples being 1.09 and 1.10.

In series C, the mean inspired concentration of isoflurane was intermediate between series A and B and showed a significant decline with time (table II).

Minute volume of ventilation

Mean minute volumes ranged from 4.58 to 4.90 litre min^{-1} for the two anaesthetics in series A and B (table III). There were no significant differences between the two anaesthetics in either series. The only significant change with time was a decrease for isoflurane in series A. Minimal values were

TABLE III. *Pulmonary ventilation.* **Not significantly different from corresponding value for halothane; † significantly different for corresponding value for halothane* (P = *0.05, Mann–Whitney test*)

		Minute volume				Tidal volume				Ventilatory frequency			
		litre min^{-1}		Regression against duration of surgery		ml		Regression against duration of surgery		b.p.m.		Regression against duration of surgery	
		Mean	SD	*r*	*P*	Mean	SD	*r*	*P*	Mean	SD	*r*	*P*
Series A	Halothane	4.64	0.49	−0.48	ns	206	15	+0.21	ns	22.6	2.2	−0.65	0.05
	Isoflurane	4.58*	0.69	−0.88	0.05	248†	26	−0.37	0.05	18.5†	2.4	−0.68	0.05
Series B	Halothane	4.64	0.59	−0.43	ns	179	11	+0.51	ns	26.0	2.9	−0.77	0.01
	Isoflurane	4.90*	0.31	+0.14	ns	226†	13	−0.29	ns	21.7†	1.3	+0.38	ns

TABLE IV. *Carbon dioxide tensions (kPa). * Not significantly different from corresponding value for halothane; † significantly different from corresponding value for halothane* (P < *0.001*) (*Student's* t *test*)

		End-tidal samples				Arterial samples					Arterial minus end-tidal				
				Regression against duration of surgery		1st sample		2nd sample		Difference 1st–2nd samples	1st sample		2nd sample		Difference 1st–2nd samples
	Volatile anaesthetic	Mean	SD	*r*	*P*	Mean	SD	Mean	SD		Mean	SD	Mean	SD	
Series A	Halothane	7.21	0.12	0.12	ns	8.00	0.99	8.40	1.54	ns	1.02	1.22	1.04	1.03	ns
	Isoflurane	7.09*	0.50	0.70	0.05	7.38*	0.91	8.18*	1.66	$P = 0.04$	0.72*	0.79	0.86*	0.44	ns
Series B	Halothane	8.13	0.14	0.71	0.05	8.61	1.38	8.30	1.10	ns	0.53	0.80	−0.07	0.56	ns
	Isoflurane	7.12†	0.15	−0.13	ns	7.18†	0.60	7.60*	0.75	$P = 0.05$	0.08*	0.47	0.30*	0.50	ns
Series C	Isoflurane	5.8	0.32			—		—		—	—		—		—

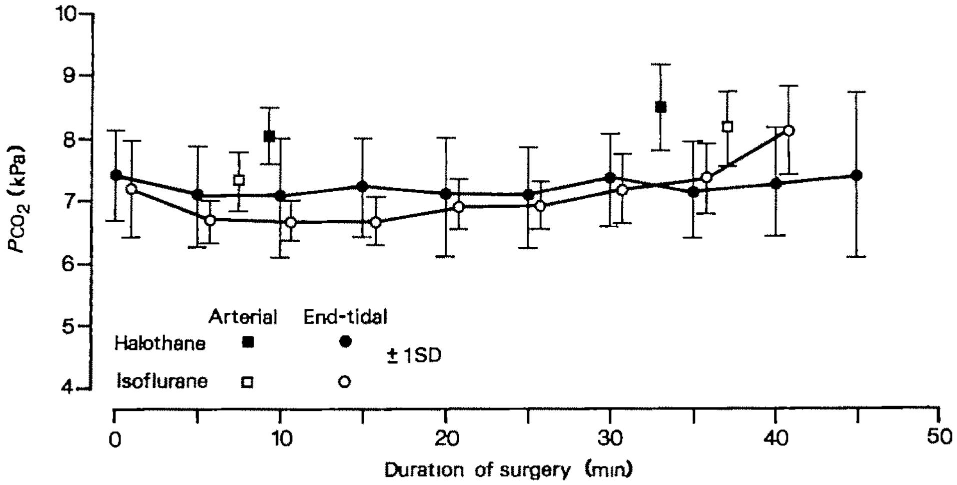

FIG. 2. End-tidal and arterial $P\mathrm{CO}_2$ as a function of duration of surgery (Series A: mean MAC = 1.39–1.43).

1.95 litre min^{-1} for halothane and 2.5 litre min^{-1} for isoflurane.

Tidal volume and frequency

Tidal volumes were significantly greater with isoflurane in both series, while the mean ventilatory frequency was significantly greater with halothane (table III). There was a significant decrease in frequency with time for halothane in both series and isoflurane in series A.

End-tidal and arterial $P\mathrm{CO}_2$

In series A the mean end-tidal values of $P\mathrm{CO}_2$ were 7.21 kPa with halothane and 7.09 kPa with isoflurane, the difference not being significant (table IV). In series B the end-tidal $P\mathrm{CO}_2$ values were 8.13 kPa for halothane and 7.12 kPa for isoflurane—the difference being significant ($P < 0.001$). At each 5-min time interval in series A, the end-tidal $P\mathrm{CO}_2$ with halothane was greater than with isoflurane except at 35 and 40 min, although the differences were not significant (fig. 2). In series B the differences were significant at seven out of nine sampling times (fig. 3). There was a small but significant increase in $P\mathrm{CO}_2$ with time for halothane in series B and isoflurane in series A. There was invariably an abrupt, although often transient, decrease in end-tidal $P\mathrm{CO}_2$ when the degree of surgical stimulation was increased (fig. 4).

Arterial $P\mathrm{CO}_2$ was greater for halothane than for isoflurane in each series at both 10 and 30 min after the beginning of surgery (table IV), but the difference was only significant in series B at

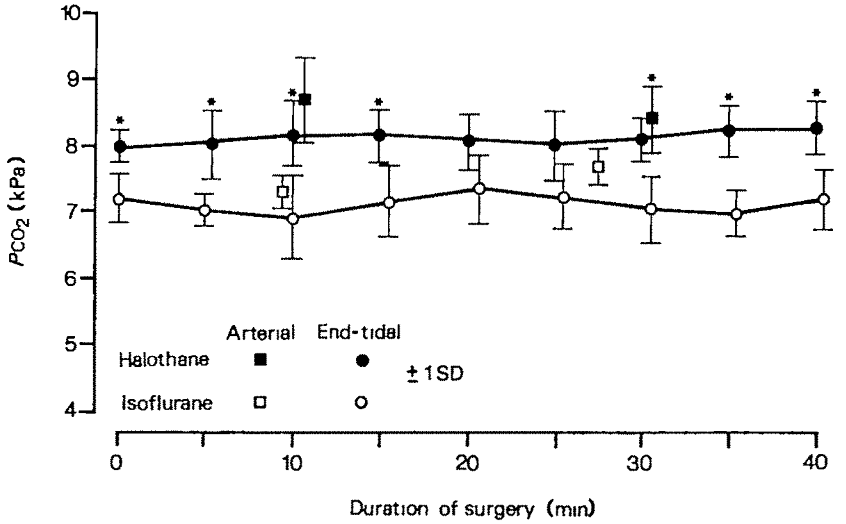

FIG. 3. End-tidal and arterial PCO$_2$ as a function of duration of surgery (Series B: mean MAC = 1.75–1.76).

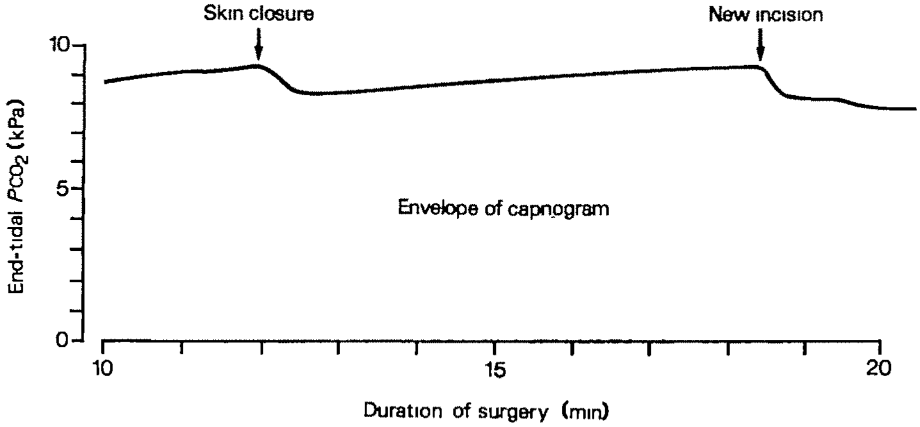

FIG. 4. The outline of the capnogram in one patient to show the time course of changes in end-tidal PCO$_2$ in relation to surgical stimulation.

10 min. There were significant increases in arterial PCO$_2$ between the 10th and 30th min in both series for isoflurane, but not halothane (figs 2 and 3; table IV). The upper limits of the 95% range were 9.98 and 11.37 kPa for halothane at 10 min in series A and B, respectively. Corresponding figures for isoflurane were 9.20 and 8.38 kPa. At 30 min the values were 11.48 and 10.5 kPa for halothane and 11.50 and 9.10 kPa for isoflurane.

In series C, there was no significant change in end-tidal PCO$_2$, up to a maximum of 225 min (figs 5 and 6). Mean tensions during surgery were significantly less than before the start of surgery, but there was no significant change during surgery. Mean PCO$_2$ was less than in series A and B, although the inspired isoflurane concentration was intermediate between the two.

The mean arterial–end-tidal PCO$_2$ gradient was 0.56 (SD 0.42) kPa and there were no consistent differences between halothane and isoflurane or between the 10th and 30th min of surgery.

Arterial PO$_2$ *and pH*

Arterial PO$_2$ was not significantly different between the two anaesthetics and the only significant change with time was a decrease of

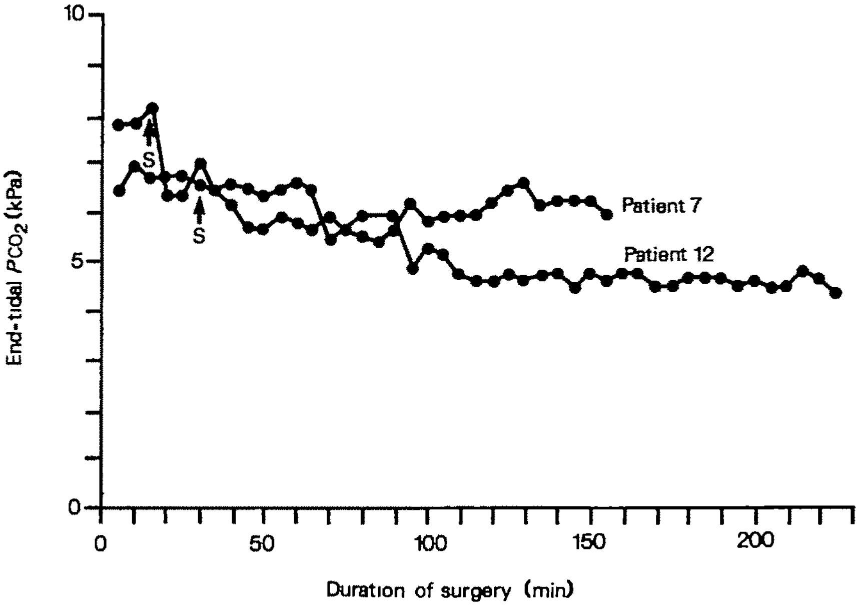

FIG. 5. End-tidal PCO_2 plotted against duration of surgery for two patients in Series C. S = Stimulation.

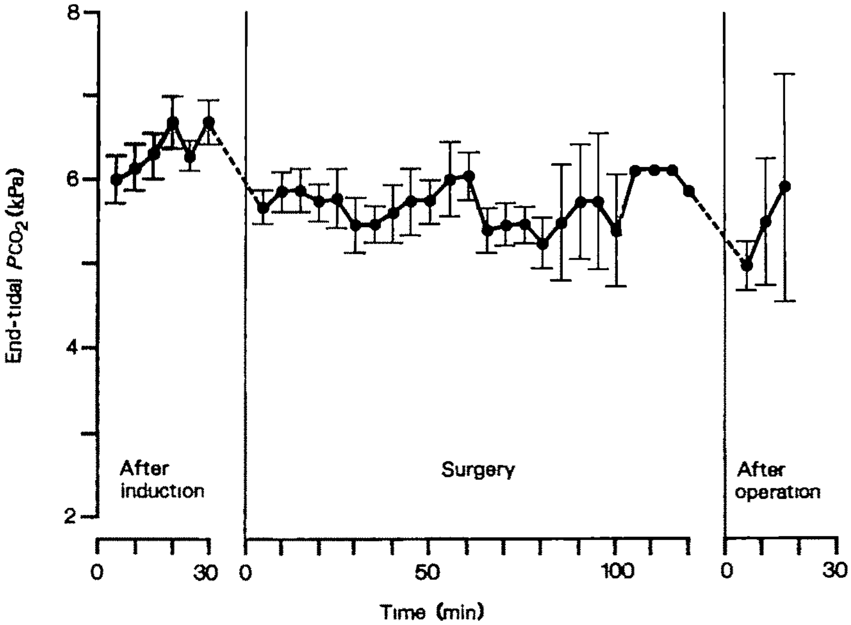

FIG. 6. End-tidal PCO_2 (mean ±1 SEM) plotted against duration of surgery for patients in series C (mean MAC = 1.52±1 SEM).

1.5 kPa with isoflurane in series A (table V). Nevertheless, arterial PO_2 was lower with isoflurane than with halothane in all four sub-groups. The distribution of PO_2 was skewed and the lowest values were 8.6 and 7.6 kPa for isoflurane in series A and B. The corresponding figures for halothane were 12.8 and 8.7 kPa, respectively.

Mean values for arterial pH in the various

TABLE V. *Arterial oxygen tensions and pH. No value for isoflurane is significantly different from corresponding value for halothane*

		Oxygen tension (kPa)					pH				
	Volatile anaesthetic	1st sample		2nd sample		Difference 1st–2nd samples	1st sample		2nd sample		Difference 1st–2nd samples
		Mean	SD	Mean	SD		Mean	SD	Mean	SD	
Series A	Halothane	14.6	1.84	15.3	1.90	ns	7.260	0.03	7.230	0.05	ns
	Isoflurane	13.1	4.56	11.6	3.71	$P = 0.5$	7.263	0.03	7.225	0.05	$P = 0.02$
Series B	Halothane	13.2	3.90	13.7	3.10	ns	7.217	0.05	7.200	0.04	ns
	Isoflurane	12.9	4.30	11.7	3.40	ns	7.252	0.02	7.240	0.03	ns

sub-groups (table V) showed no significant difference between halothane and isoflurane. The only significant difference between 10 and 30 min after the start of surgery was a reduction of 0.038 for isoflurane in series A. The lower limits of the 95% confidence range for halothane at 10 min were 7.20 and 7.12 in series A and B. The corresponding figures for isoflurane were 7.20 and 7.21. At 30 min, the values were 7.13 and 7.12 for halothane and 7.13 and 7.18 for isoflurane.

DISCUSSION

The maintenance of a normal respiratory acid–base status depends on the adequacy of alveolar ventilation in relation to the production of carbon dioxide. The former is determined by pulmonary ventilation and deadspace. Ventilation depends on the balance between pharmacological depression and surgical stimulation (Eger et al., 1972; France et al., 1974). Physiological deadspace is usually increased by anaesthesia (Campbell, Nunn and Peckett, 1958) but the effects of surgery are unknown. Carbon dioxide production is depressed by anaesthesia (Nunn and Matthews, 1959) but France and co-workers (1974) reported a 25% increase in carbon dioxide production in association with surgical stimulation. The resultant Pa_{CO_2} during anaesthesia is thus difficult to predict and is further influenced by the time required to attain a steady state (Nunn and Matthews, 1959). In this study we compared the net effects of these factors on the respiratory status of patients anaesthetized according to current practice with either isoflurane or halothane for routine surgery.

In series A, the mean end-tidal concentrations of the two anaesthetics were maintained at approximately equal MAC-multiples by use of a mass spectrometer. The ratios of end-tidal to inspired concentrations remained remarkably constant for each agent during the period of the observations and the expected increases in the ratios could not be detected (Eger, 1974). This was probably because of the high inspired concentrations which were used early in the course of the anaesthetic to obtain a rapid approach to the target end-tidal concentration. However, the mean ratios differed significantly for the two agents in accord with their blood solubility, and the consistency of the results appeared to be sufficient for prediction of end-tidal concentrations from the more easily measured inspired concentrations.

The ratios of inspired to end-tidal concentrations observed in series A were used to estimate the end-tidal concentrations in series B. It appeared that the anaesthetists came very close to obtaining equal MAC-multiples of the two agents on the basis of clinical judgement. However, for both anaesthetic agents, a deeper level of anaesthesia was selected when the end-tidal concentrations were not known. It appeared that the use of the mass spectrometer permitted the use of lower concentrations of anaesthetic agent. However, the differences in MAC values between the three series were too small to have any significant effect on respiratory variables.

Although the minute volumes were not significantly different for the two anaesthetics, ventilatory frequency was significantly less with isoflurane, as was reported by France and co-workers (1974). Tidal volume was correspondingly greater.

At approximately equal MAC-multiples and under the conditions of this study, the mean end-tidal and arterial P_{CO_2} were almost always higher with halothane than with isoflurane and the differences were statistically significant in many of the sub-groups. This was also true for the upper limit of the 95% confidence range of P_{CO_2}. This may have been a result of the relative sparing of tidal volume with isoflurane (table III). Thus alveolar ventilation may have been greater with isoflurane even though the minute volumes were not significantly different.

Although there were statistically significant increases in $P\text{CO}_2$ with duration of surgery in some groups, the changes were small and not clinically significant. $P\text{CO}_2$ always increased during the 20 min of anaesthesia before the start of surgery, but the onset of surgical stimulation caused a rapid decrease in $P\text{CO}_2$, in spite of relatively deep levels of anaesthesia, sufficient to prevent any overt movement of the patient. There was no significant increase in end-tidal $P\text{CO}_2$ during the longer anaesthetics in series C. In part this may have been a result of the waning effect of the opioid premedication.

With both anaesthetics, the mean $P\text{CO}_2$ was increased and the mean values were well above the upper 95% confidence limit of the normal reference range (6.1 kPa). $P\text{CO}_2$ values above 10 kPa were not unusual. Respiratory acidosis during anaesthesia with spontaneous ventilation has long been recognized, although values in the present study are higher than in our two earlier studies (Nunn and Hill, 1960; Nunn, 1964), in which the mean values for arterial $P\text{CO}_2$ were 6.9 and 6.4 kPa, respectively; there were no values greater than 9.4 kPa.

Eger and colleagues (1972) reported a mean arterial $P\text{CO}_2$ of 8.2 kPa at 1.3 MAC multiples of isoflurane in unpremedicated patients without surgical stimulation and 6.5 pKa during operation. With 70% nitrous oxide the corresponding values at 1.4 MAC multiples were 6.9 and 5.9 kPa. In unstimulated, unpremedicated volunteers, Dolan and co workers (1974) reported values of about 7.6 kPa with isoflurane alone at 1.4 MAC multiples and 7.2 kPa with nitrous oxide and isoflurane at the same MAC-multiple. Values for $P\text{CO}_2$ in our study tend to be higher than the corresponding figures in these studies. This was probably attributable to the opiate premedication which our patients had received.

Lam and associates (1982) postulated that the beneficial effect of using nitrous oxide in the carrier gas arose from the partial substitution of an anaesthetic with less respiratory depressant effect. However, studies of hyperbaric nitrous oxide suggest that nitrous oxide has a respiratory depressant effect little different from that of isoflurane (Eger, 1981). There is ample evidence that surgical stimulation limits the increase in arterial $P\text{CO}_2$ (Eger et al., 1972; France et al., 1974).

The mean arterial–end-tidal $P\text{CO}_2$ difference of 0.56 kPa is close to the value of 0.67 kPa reported for patients under similar circumstances by Ramwell (1958) and 0.61 kPa by Nunn and Hill (1960). There was no significant trend with time and no significant difference between the two anaesthetics.

The study was not designed to measure alveolar oxygen tensions which would have remained well above the normal value of 14 kPa with an inspired oxygen concentration of approximately 30%, and should have been of the order of 20 kPa. However, mean arterial $P\text{O}_2$ values, in the range 11.6–15.3 kPa, were comparable to those reported by Nunn (1964) suggesting a similar alveolar–arterial $P\text{O}_2$ gradient. The lowest arterial $P\text{O}_2$ was 8.7 kPa with halothane and 8.2 kPa with isoflurane. Since $P\text{CO}_2$ values were generally lower for isoflurane, alveolar $P\text{O}_2$ was probably greater. Therefore, it seems possible that alveolar–arterial $P\text{O}_2$ gradients were greater with isoflurane, but this was not measured in our study.

Arterial pH values were not significantly different for the two anaesthetics, but the departure from normality was considerable and there were many values in the range 7.1–7.2 which, in relation to the simultaneous values for $P\text{CO}_2$, indicated slight metabolic acidosis in addition to the respiratory acidosis.

CONCLUSION

Taking series A and B together, there is no evidence to suggest that the use of isoflurane for anaesthesia with spontaneous ventilation results in higher $P\text{CO}_2$ values than with halothane. Indeed, they are likely to be lower. Furthermore, we found no evidence of a clinically significant increase in $P\text{CO}_2$ with time. Nevertheless, the study reconfirmed the considerable degree of hypercapnia which usually occurs during anaesthesia with spontaneous breathing. Monitoring the end-tidal concentrations of the anaesthetics resulted in the use of lower MAC values of both anaesthetics.

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PROSPECTIVE, MULTI-CENTRE TRIAL OF MORTALITY FOLLOWING GENERAL OR SPINAL ANAESTHESIA FOR HIP FRACTURE SURGERY IN THE ELDERLY

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Fracture of the upper femur is a common injury in the elderly. The reported hospital mortality following its surgical correction has varied between 2.7% and 28% (McLaren, Stockwell and Reid, 1978; Goucke, 1985). It is more than 20 years since the effect of anaesthesia on mortality in these patients was first compared prospectively (Gauthier and Hamelberg, 1963). However, it was McLaren, Stockwell and Reid (1978) who first suggested that subarachnoid block (SAB) was associated with a reduced early mortality compared with general anaesthesia (GA) for internal fixation procedures. Subsequently, neither McKenzie and colleagues (1980) nor Davis and Laurenson (1981) could demonstrate a statistically significant difference, although in both studies mortality was less following SAB. In our opinion at that time, none of these studies was sufficiently large epidemiologically. Therefore, we planned a large multi-centre prospective randomized trial to re-examine the effect of anaesthesia on mortality in these elderly patients. This paper presents the results of that investigation.

SUMMARY

In a prospective randomized multi-centre study, the mortality following internal fixation surgery for fracture of the upper femur was investigated in 538 elderly patients allocated to receive subarachnoid blockade or general (narcotic–relaxant) anaesthesia. The 28-day mortality was 6.6% with subarachnoid, and 5.9% with general, anaesthesia. The difference was not significant (95% confidence limits: −3.5 to +4.8). At 1 year following surgery, the mortality was 20.4%. Increasing age, ischaemic heart disease, cardiac failure, preoperative arrhythmias and poor ASA status were all associated with increases in early and long term mortality. A delay to surgery of more than 24 h from admission was also associated with an increased 28-day mortality. Senile dementia and admission other than from the patient's own home, were factors associated with a poorer long term outcome. From the point of view of mortality, subarachnoid anaesthesia did not appear to confer any advantages over general anaesthesia in non-prosthetic surgery for hip fracture in the elderly.

PATIENTS AND METHODS

The study was formulated on a multi-centre basis and co-ordinated from Christchurch. It was approved by the Ethics Committee of each of the five participating hospitals. For all or part of the period from June 1982 to September 1984, patients undergoing internal fixation procedures for trochanteric or subcapital fracture of the femur were considered for the trial unless one or more of the following were present: age less than 55 yr;

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TABLE I. *Basic anaesthetic techniques for spinal or general anaesthesia in 538 elderly patients undergoing emergency hip surgery*

Spinal anaesthesia	General anaesthesia
Premedication: none except i.m. opioid analgesia as indicated Monitor: heart rate, arterial pressure, ECG Pre-load with Hartmann's solution 2–400 ml	
Supplementary oxygen Sedation: Benzodiazepine (i.v. analgesia optional) Spinal: Tetracaine, nupercaine or bupivacaine (optional) Hyper/iso-baric Lumbar injection	Pre-oxygenation Induction: i.v. (usually thiopentone) Tracheal intubation (± suxamethonium) Maintenance: Fentanyl Non-depolarizing neuromuscular blocker N_2O/O_2 (2:1) IPPV/normocarbia (avoid halothane/droperidol if possible) Reversal: Neostigmine and atropine
1. I.v. fluids and blood as clinically indicated 2. Sympathomimetic as required (usually ephedrine) 3. Accurate and full anaesthetic record	

multiple trauma; possible replacement hemi- or total arthroplasty; pathological fracture.

Patients could also be excluded from the trial, but only *before* randomization, at the discretion of the anaesthetist if a specific contraindication to either SAB or GA were present. However, information on these, and any other patients excluded from the trial for whatever reason, including refusal, was documented in the postoperative period—to assess the rate of inclusion and any bias to patient selection.

Once they had been assessed for anaesthesia, patients suitable for inclusion in the trial were randomly allocated to receive either SAB or GA, the sexes being randomized separately within each hospital. In all other respects the patients were treated according to current practice in the respective hospitals. The design of the study was broad and allowed some latitude in the precise details of the two anaesthetic techniques, while requiring adherence to certain specific principles of management (table I). Patients in whom satisfactory SAB could not be established received GA. However, for statistical evaluation they were retained in the SAB group as advocated by Peto and co-workers (1976).

The anaesthetist completed pre- and intraoperative data sheets for each patient. Information included demographic details, past medical history, ASA status, (ASA, 1963) and concomitant disease, social status and details of the course of anaesthesia.

The postoperative follow-up (at 28 days) of each patient was the responsibility of one anaesthetist at each hospital. Postoperative complications, as recorded in the medical notes, and the duration of postoperative stay in the acute orthopaedic ward were recorded. All deaths during that time were documented. Postmortem confirmation of the cause of death was sought, whenever possible.

Long term follow up of the New Zealand patients (89% of the total) was based on the New Zealand Register of Births, Deaths and Marriages of the Justice Department as at December 31, 1984. Postoperative follow up therefore varied from 3 to 30 months, depending on the date of surgery.

Statistical Methods

The study was formulated using the recommendations in the report to the Medical Research Council's Leukaemia Steering Committee (Peto et al., 1976) for the design and analysis of multicentre randomized clinical trials requiring prolonged observation of the patient.

The planned sample size ($n = 506$) was calculated on the basis of previous mortality figures as sufficient to provide an 80% chance of detecting a halving of the 28-day mortality from 16% in the GA group to 8% in the SAB group (Cohen, 1977). The trial was stopped just after this planned sample size (actual $n = 549$). Statistical analysis was carried out using the BMDP statistical package (Dixon, 1981).

The two anaesthetic groups were compared on the preoperative descriptor and prognostic vari-

TABLE II. *The numbers of patients from each centre, female/male ratios and anesthetic techniques used*

Hospital (period of study)	Patients	Female/male ratio	General anaesthesia	Subarachnoid blockade
Auckland (7/82–2/84)	38	3.2:1	19	19
Christchurch (6/82–9/84)	313	2.9:1	164	149
Dunedin (6/82–9/84)	97	4.7:1	46	51
Nelson (6/82–9/84)	33	16:1	17	16
Perth (2/84–9/84)	57	3.4:1	33	24
Total	538	3.5:1	279	259

ables using *t* tests or Chi-squared tests of independence. The effect of individual prognostic variables on mortality over the entire period of the study was investigated by survival analysis, using the Mantel–Cox test statistic. The short-term effect of each variable was investigated by Chi-squared tests on survival or death by 28-days.

From the above univariate analyses, two subsets of variables were extracted as the most important predictors of short-term and long-term survival, respectively. These two subsets of variables were then used as covariates when comparing survival in the two anaesthetic groups. The analysis of long-term survival involved placing the anaesthetic variable in the Cox proportional hazards model using the Wald test statistic. The effect of the anaesthetic technique up to 28-days was measured by placing the concomitant variables into a logistic regression.

To estimate the relative hazards for these patients, observed deaths were compared with expected deaths calculated by the person–years method. Only New Zealand patients were included in this analysis. The New Zealand Department of Statistics (1985) provided central death rates for each age and sex—based on the years 1980–82. Exact dates of entry and death or censoring were available but, as ages were given in whole years, age x was assumed to be $x+1/2$.

RESULTS

Patient selection

A total of 549 patients were entered into the trial. Eleven were excluded because one or more of the exclusion criteria were present, leaving 538 patients for analysis (table II). The relatively large input from Christchurch represents case collection in a busy general hospital over the whole period of the trial. The contributions from the other centres were drawn over shorter periods, or from hospitals with a lower throughput of upper femoral fractures.

TABLE III. *Mean (SD) age, weight and ASA grading (expressed as % patient total) for each sex in 538 elderly patients with hip fracture*

	Males	Females	All patients
Age (yr)	77.1 (9.8)	80.2 (8.4)	79.5 (8.8)
Weight (kg)	66.0 (10.1)	57.1 (11.4)	59.2 (11.7)
ASA Grade			
I or II	32%	46%	43%
III	54%	46%	48%
IV	14%	8%	9%

The ages, weights and ASA gradings (table III) were similar in each hospital, with the exception of Nelson. The Nelson patients were older (mean 81.5 yr, SD 7) and sicker (30% of patients ASA grade IV) than those in the other centres. Twenty percent of the included patients had subcapital and 80% trochanteric fractures. The patients with subcapital fracture were equally distributed between the sexes and the two anaesthetic groups and there were no statistical differences in preoperative status or intraoperative course between them and the patients with trochanteric fractures.

Anaesthetic management

In the 259 patients in the SAB group, attempts at lumbar puncture were unsuccessful in 30 patients (11.5%) and an incomplete block requiring additional analgesia of some form occurred in 14 patients (5.4%).

Hypotension, defined as a decrease in systolic

TABLE IV. *The 28-day mortality (%) for each anaesthetic group shown for each hospital, and overall*

	Subarachnoid blockade mortality (%)	General anaesthesia mortality (%)	Overall mortality (%)
Auckland	10.5	5.3	7.9
Christchurch	6.1	6.3	6.2
Dunedin	5.9	0	3.1
Nelson	18.8	11.8	15.2
Perth	0	11.1	5.9
Total	6.6	5.9	6.3

arterial pressure of more than 20% of the pre-induction value persisting for more than 10 min, occurred in 38% of the SAB group and 24% of the GA group. Of the SAB patients who exhibited hypotension, 82% received a sympathomimetic drug whereas only 2.5% of the hypotensive patients in the GA group did so.

There was one non-fatal anaphylactoid reaction at induction of general anaesthesia. No intra-operative death occurred.

Anaesthetic technique and 28-day mortality

The overall 28-day mortality was 6.3% (table IV); 6.6% in the SAB group and 5.9% in the GA group. The difference in mortality was not statistically significant (95% confidence limits for the difference between the groups: −3.5% to +4.8%).

The individual hospital figures, except for those from Christchurch, appear to show differences in mortality; however, these did not reach statistical significance at the 5% level, and did not consistently favour either anaesthetic technique. The overall mortality from Nelson, both 28-day and long term was significantly higher than that from the other hospitals, but this was related to the poorer preoperative clinical state, particularly the presence of pneumonia, in this group and not to differences in management.

In the "failed spinal" patients the mortality rate did not differ from that of the series as a whole. There was no difference in the 28-day mortality between patients with trochanteric fractures and those with subcapital fractures.

Anaesthetic technique and long-term mortality

The mortality at 1 year was 20.4% and there was no difference in long-term mortality between the two anaesthetic groups. The relationship between the observed and the expected mortality rates is shown in table V. There was a significantly higher mortality during at least the first 6 months following surgery when compared with the general population matched for age and sex. This was most marked in the first month when the observed mortality was nine times that expected. There was no difference in long-term outcome between trochanteric and subcapital fractures.

Factors related to mortality

Several preoperative factors including the age of the patient and ASA grading were found to relate to increased mortality both within 28 days of surgery and long-term. These are listed in table VI. Several postoperative complications were also associated with a higher mortality (table VI). When the preoperative high risk factors indicated by an asterisk in table VI were included in the mortality analysis, there was still no difference in either 28-day or long-term mortality between the two anaesthetic groups.

Factors not related to mortality

Factors that appeared unrelated to either 28-day or long-term mortality included a history of hypertension or CNS disease other than dementia. Although the mortality was slightly higher in

TABLE V. *Observed and expected numbers of deaths in elderly patients following emergency hip surgery for time periods up to 2.5 years after operation* ($n = 479$, *New Zealand only*). $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.002$

Period	Observed no. of deaths	Expected no. of deaths	Observed:expected ratio	Cumulative mortality
1st month	31	3.5	9.0***	6.3%
2nd month	19	3.6	5.2***	10.4%
3rd month	10	3.4	2.9**	12.5%
4th–6th month	17	9.1	1.9*	16.0%
7th–12th month	21	15.8	1.3	20.4%
Over 12 months	22	19.3	1.1	25.1%
Total	120	54.6	2.2	—

TABLE VI. *The pre- and postoperative factors associated with increased 28-day and long-term mortality in elderly patients with hip fracture.* Inclusion in mortality analysis did not produce a difference in either mortality between groups*

	Mortality	
	28-Day	Long-term
Preoperative factors	1. Ischaemic heart disease* 2. Cardiac failure* 3. Cardiac arrhythmias on ECG* 4. ASA grade III or IV* 5. Age; especially > 85 yr	1. ASA grade III or IV* 2. Cardiac arrhythmias on ECG* 3. Ischaemic heart disease* 4. Dementia 5. Cardiac failure 6. Admission other than from patient's own home 7. Surgical delay over 24 h from admission 8. Age
Postoperative factors	1. Cerebrovascular accident 2. Pneumonia 3. Renal failure	1. Cerebrovascular accident 2. Pneumonia 3. Renal failure

men, the difference between men and women was not statistically significant either in terms of crude survival or in terms of deaths relative to those expected from population life-tables taking into account age and sex. Neither the type of fracture nor the occurrence of intraoperative hypotension (as defined above) appeared to influence the outcome. The diagnosis of postoperative thromboembolic disease was based on clinical signs only and, therefore, its contribution to mortality could not be assessed. Pulmonary embolism was clinically diagnosed in 1.5 % of patients.

Cause of death

There were 33 deaths within 28 days in the whole group, but only 10 patients underwent postmortem examination. In 26 cases the cause of death could be ascertained either from postmortem or the patient's medical records. These are shown in table VII.

Duration of hospital stay

In 524 patients the duration of postoperative stay in the acute hospital was recorded. The mean (SD) hospital stay was 15.7 (9.6) days for the SAB group, and 15.9 (9.0) days for the GA group. There was no significant difference between the two groups.

Patients missed from the trial

There were 57 patients from the New Zealand centres (11.9 % of the total included) who met all the inclusion criteria but, for a variety of reasons, were excluded from the trial. Four patients (7 %) died within 28 days. Of this group of 57 patients, 40 received GA of whom two died, and 17 received SAB of whom two died. These mortality rates do not differ statistically from each other or from the 538 patients included in the trial, confirming that no undue bias in patient selection had been introduced to the study.

DISCUSSION

Since McLaren, Stockwell and Reid (1978) reported a significant reduction in the 28-day mortality following SAB (7 %) compared with GA (28 %), the influence of anaesthesia on mortality following hip fracture surgery has been much debated. McKenzie and colleagues (1980) in a study of 100 patients found a 28-day mortality of 15.7 % following GA compared with 10.2 %

TABLE VII. *Recorded cause of death in 26 of the 33 patients who died within 28 days after operation. No data were obtainable for the other seven patients*

Cause of death	General anaesthesia	Subarachnoid blockade	Total
Pneumonia	4	5	9
Myocardial infarction	1	2	3
Ischaemic heart disease and cardiac failure	3	3	6
Cerebrovascular accident	0	3	3
Renal failure	0	1	1
Pulmonary embolus	1	0	1
Peptic ulcer	0	1	1
Carcinoma	1	1	2
Total	10	16	26

following SAB. Davis and Laurenson (1981), reporting on 132 patients, observed a 28-day mortality following GA of 13.2%, compared with 4.6% following SAB. In neither study did the mortality difference reach statistical significance at the 5% level. McKenzie, Wishart and Smith (1984) studied a further 150 patients and observed that SAB significantly decreased the 14-day mortality, compared with GA following femoral neck surgery, but that by 2 months after the operation no difference in mortality was evident between the groups.

More recently, Valentin and associates (1986) have presented data from 578 patients randomly allocated to SAB or GA in whom the overall mortality at 30 days was 7% and in whom no difference in mortality was present between the two anaesthetics. In the present study of 538 patients, the 28-day mortality was virtually the same at 6.3% and we have also been unable to demonstrate any difference in acute mortality related to anaesthetic technique.

The appropriate sample size for a study depends on the expected mortality rates (Cohen, 1977). The present study was planned using 28-day mortality rates suggested by the literature and our previous work. However, the actual mortality in the GA group was less than half that expected (6% *v.* 16%). The planned sample size gave power of 80% to detect (two-tailed) a reduction in mortality from 16% (GA) to 8% (SAB), but power of only 50% to detect a reduction from 8% to 4%. Over 1000 patients would be necessary to achieve power of 80% for that difference. Thus, as overall mortality decreases it is increasingly difficult to detect differences resulting from anaesthetic technique, even though there may be an effect in conditions of higher mortality.

The reported mortality rate following femoral neck fracture has varied widely (Goucke, 1985). However, our overall 28-day mortality at 6.3% is very similar to that reported in recent major epidemiological studies (Dahl, 1980; Jensen, 1981; Kenzora et al., 1984; Valentin et al., 1986). Whilst marked variations may be seen when mortality at only one point in time is measured, these tend to disappear when long-term outcome is considered. For instance, the very low 28-day mortality (2.7%) reported by Goucke (1985) reaches 20.8% 1 year after the operation—a value which is the same as that for both our patients (20.4%) and those of Valentin and associates (1986) (19%).

As can be seen from figure 1, the cumulative mortality followed very similar trends in the two anaesthetic groups throughout the follow-up period. At no stage was there evidence of a differing mortality rate between the two as reported by McKenzie, Wishart and Smith (1984) in their patients. Both ours and the Hellerup study (Valentin et al., 1986) appear to illustrate the widely recognized phenomenon in prospective studies of mortality of the observed mortality rates being lower than predicted.

The results from the individual hospitals taking part in this trial illustrate how small series can

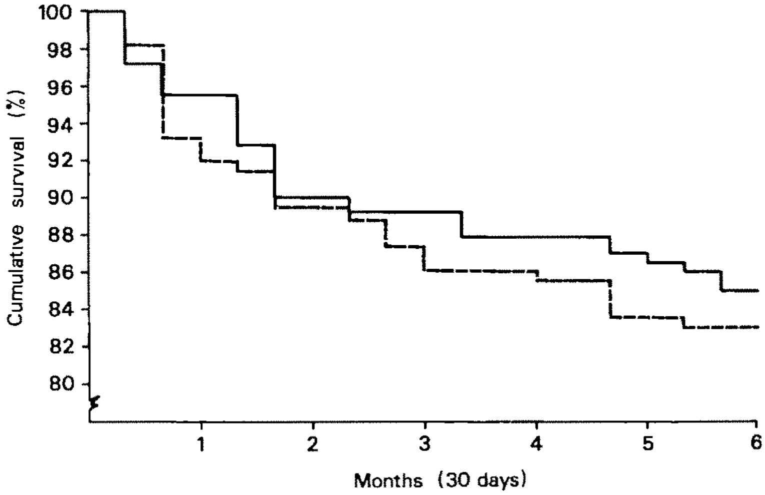

FIG. 1. The cumulative mortality over the first 6 months following surgery. There were no differences between the two anaesthetic groups (— = GA; --- = SAB).

produce results suggestive of a major effect when this is not confirmed in the series as a whole. In multicentre trials there is no assumption that the type of patient or quality of management is comparable in all centres. It is only assumed that if a treatment is of medical value, then this will be true at every centre and, although the treatment difference actually observed in an individual centre may be randomly obscured or even reversed, the overall sum of all the separate treatment differences, one from each centre, should point in the right direction and the separate differences should thus reinforce each other, even if most, or perhaps all, of the separate differences are not individually significant (Peto et al., 1976).

Despite the very similar results there are certain methodological differences between our own and the Hellerup studies. Whilst the Cox proportional hazards model was used in both, we attempted to take into account well-defined risk factors in the analysis. We specifically excluded patients undergoing prosthetic surgery, although many of our patients with subcapital fractures would probably have undergone Moore's hemiarthroplasty at Hellerup. Overall, the balance of patients is not quite the same in the two studies.

A much more important difference relates to the handling of "failed" SAB. In the present study 11.5% of the patients were originally allocated to receive SAB, but required GA because of the failure to establish adequate blockade. These were retained in the SAB group for statistical analysis. In the Hellerup group the failure rate was also approximately 10%, but they chose to exclude these patients from their analysis after randomization. We consider it correct statistically to retain them in the original random allocation group for mortality analysis on an "intention to treat" basis as advocated by Peto and co-workers (1976). The outcome in these patients must be included in the SAB group if we are to have a realistic appraisal of the effect on mortality were subarachnoid anaesthesia to be routinely used for this form of surgery. In addition, because their follow-up was not reported, the Hellerup group make assumptions about their excluded patients not unduly biasing their study, which may or may not be true. Since we followed the 57 patients who met all the inclusion criteria for the study but were excluded for various reasons before randomization, we can be fairly certain that no undue bias resulted in the present study.

From a practical viewpoint, it would appear from these two large studies that there is a quite high failure rate with spinal anaesthesia in elderly patients with hip fracture when the clinical practice of a large number of anaesthetists with a wide range of experience (including many junior trainees) is reviewed in this way. This contrasts with studies in which spinal anaesthesia has been performed by only one anaesthetist, or a few experienced anaesthetists, when a failure rate of less than 5% has usually been the case. Such practical differences must always be borne in mind when advocating general policies for patient management based on tightly defined and carefully controlled experimental work.

We believe that the present study and that of the Hellerup group (Valentin et al., 1986) realistically represent the clinical situation if a general policy of SAB for femoral neck fracture surgery were implemented in a busy hospital or hospital group. In these circumstances anaesthetists differ in details of anaesthetic management and the patients may be under the care of one of several surgical teams. Having said this, we found from examination of the anaesthetic records that there was a reassuring uniformity of management and that the design of the study was faithfully adhered to by our colleagues.

Many factors have been reported to be associated with increased mortality after surgery for fracture of the femoral neck. These include age and male sex (Gallanaugh, Martin and Millard, 1976), preoperative physical status and activity (Barnes et al., 1976), preoperative nutritional status (Bastow, Rawlings and Allison, 1983), delay between injury and surgery for whatever reason (Aldrete, Davis and Hingson, 1967), fracture type and operative procedure undertaken (Chan and Hoskinson, 1975; Barnes et al., 1976), preoperative cerebral dysfunction (Miller, 1978), and postoperative morbidity (Kenzora et al., 1984).

Our data are consistent with these reports in that the most important factors demonstrated in the present study were age, cardiovascular disease, ASA grading and cerebral dysfunction. We differ from the Hellerup group only in not seeing a difference in mortality related to sex or to the type of fracture in our patients.

Zindrick and co-workers (1985) found, in a careful 10-year retrospective review, that there appeared to be a tendency for older, less healthy patients to have been treated with primary hemiarthroplasty. They suggested that the previously reported increased postoperative morbidity and mortality associated with this procedure (as compared with internal fixation) may be a result of biased patient selection. A similar bias could explain why, in the Hellerup study, a difference in mortality related to the fracture was seen, which was absent from our study, since the Hellerup study contained hemiarthroplasty procedures whilst ours did not.

Postoperative thromboembolism has been widely regarded as the leading cause of death in these patients (Sevitt and Gallagher, 1959). In the present study, which was based only on clinical signs and limited postmortem data, no evidence of a high contribution of thromboembolism to mortality was seen. Nevertheless, the incidence of deep vein thrombosis does appear to be significantly reduced by subarachnoid anaesthesia (Davis, Quince and Laurenson, 1980; McKenzie et al., 1985). It has been suggested that this might explain the increased mortality with general anaesthesia observed by McKenzie, Wishart and Smith (1984) in the first 2 weeks following surgery. Re-analysing their data (see Appendix) we observed that the mortality in their SAB group was significantly higher than in the GA group in the 3rd and 4th weeks after operation. If these mortality patterns are related in any way to thromboembolic disease, as suggested, then the more likely postulate is that spinal anaesthesia, like low-dose heparin in total hip replacement arthroplasty (Sikorski, 1984), merely delays the onset of deep vein thrombosis rather than preventing it. This has yet to be tested.

Our results, like those of Valentin and colleagues (1986), support the conclusion that when general anaesthesia has a low mortality, subarachnoid anaesthesia will probably not offer additional advantages. A difference in either acute (28-day) or long-term survival following spinal or general anaesthesia in elderly patients undergoing internal fixation surgery for fractures of the neck of femur has not been verified in this study.

APPENDIX

McKenzie, Wishart and Smith (1984) analysed differences in mortality rates at different time intervals by repeated applications of Chi-squared tests, thus increasing the likelihood of a Type I statistical error. We re-analysed the data from their figure 1 in intervals of 0–14 days and 15–49 days, these intervals being chosen to provide expected deaths > 5. Pearson's conditional Chi-squared test for truncated data (Elandt-Johnson and Johnson, 1980) was significant over both periods ($\chi^2 = 5.7$ and 5.9 respectively, $P < 0.02$). Thus there was a significantly higher general anaesthetic mortality in the first 2 weeks and higher spinal anaesthesia mortality in the next 4 weeks. Varying the upper end of that interval had little effect. Naturally, the Mantel–Haenzel test over these periods was not significant ($\chi^2 = 0.01$, $P > 0.9$) because it tests for consistent differences (Elandt-Johnson and Johnson, 1980) which in this case were not present.

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RELATIONSHIP OF POST-TETANIC COUNT AND TRAIN-OF-FOUR RESPONSE DURING INTENSE NEUROMUSCULAR BLOCKADE CAUSED BY ATRACURIUM

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The short duration of action and rapid recovery rate of the non-depolarizing neuromuscular blocking agent atracurium (Hughes, 1985) has increased the need for reliable methods to assess objectively the degree of neuromuscular blockade. The ability to predict, in advance, the time for clinical recovery would ensure the precise timing of incremental doses and, hence, smoother clinical neuromuscular blockade.

Mechanical responses to single twitch, tetanic and train-of-four (TOF) nerve stimulation are often used to assess recovery from neuromuscular blockade (Ali and Savarese, 1976). During intense blockade, there is no response to these modes of stimulation, and the degree of blockade cannot be established (Viby-Mogensen, 1982). However, it is possible to quantify part of this so called "period of no response" by applying tetanic stimulation (50 Hz for 5 s) followed by single twitch (1-Hz) stimulation. The number of responses to the post-tetanic single twitch stimulation is called the post-tetanic count or PTC (Viby-Mogensen et al., 1981).

It has been shown that there is a close correlation between PTC and recovery from intense neuromuscular blockade caused by pancuronium (Howardy-Hansen et al., 1984).

The objective of this study was to clarify whether a similar correlation exists between PTC and recovery from blockade caused by atracurium.

SUMMARY

Atracurium-induced intense neuromuscular blockade was evaluated in 60 randomly selected patients using the post-tetanic count (PTC) and train-of-four (TOF) methods. Thirty patients were anaesthetized with thiopentone, nitrous oxide and halothane, and 30 patients received thiopentone, nitrous oxide and fentanyl. In all patients, the response to post-tetanic single twitch stimulation appeared before the response to TOF stimulation, and a close correlation was found between the number of post-tetanic twitches (PTC) and the time interval between the PTC and the first detectable TOF response. A PTC of zero indicated that the time to first response to TOF stimulation was always more than 8 min. A PTC of 1 meant that the TOF response would appear in, on average, 9 min (95% confidence limits: 4–14 min). Halothane significantly prolonged the time from injection of atracurium to the first response to post-tetanic single twitch stimulation. It is concluded that the relationship between PTC and the time to first response to TOF nerve stimulation makes the PTC method a valuable supplement to TOF nerve stimulation for neuromuscular monitoring during clinical anaesthesia involving atracurium.

PATIENTS AND METHODS

Sixty surgical patients (32 male, all ASA Class I or II) were included in the study. Informed consent was not sought, since neuromuscular monitoring was considered routine and did not pose any risk to the patients. The study was

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approved by the College of Medicine Research Centre of our institution.

The patients were allocated randomly to two groups of 30 patients each. All patients were given lorazepam 2–3 mg by mouth 2 h before induction. Anaesthesia was induced with sodium thiopentone 3–5 mg kg^{-1}. Patients in group 1 were allowed to breathe 1–2% halothane in 50% nitrous oxide and 50% oxygen. Group 2 did not receive halothane, and anaesthesia was maintained with 70% nitrous oxide in oxygen and fentanyl 2–3 μg kg^{-1} i.v.

Neuromuscular monitoring commenced immediately after induction. The ulnar nerve was stimulated using surface electrodes and the mechanical response of the adductor pollicis muscle recorded using the Myograph 2000 neuromuscular transmission analyser. TOF nerve stimulation (repeated at 10-s intervals) was used. After supramaximal stimulation was achieved, a bolus of atracurium 0.6 mg kg^{-1} was injected i.v. The trachea was intubated and the lungs ventilated using a tidal volume of 10 ml kg^{-1} at a rate of 12 b.p.m.

At 6-min intervals, tetanic stimulation (50 Hz) was applied for 5 s followed by a 3-s pause. On each occasion the tetanic stimulation was preceded by a 1-min period of 1-Hz stimulation, which was continued after the 3-s pause. When there was no response to the 1-Hz stimulation or the observed response had faded to zero, TOF mode of stimulation was reinstituted until 1 min preceding the next tetanic stimulation (Viby-Mogensen et al., 1981). The cycle was repeated until 6 min after the first detectable response to the first stimulus in the train-of-four (TOF).

RESULTS

The two groups were similar in respect of age and weight (table I).

The first responses to post-tetanic twitch stimulation (PTTS) were seen at mean times of 34.4 and 30.3 min after the injection of atracurium in groups 1 and 2, respectively ($P < 0.05$, table I). In comparison, the first detectable response to TOF stimulation appeared after mean times of 41.9 min (group 1) and 38.1 min (group 2) (ns). When no response to PTTS was seen, time to first detectable response to TOF nerve stimulation was always more than 8 min. The mean numbers of post-tetanic twitches at the time of the first detectable response to TOF stimulation were 7.6 in group 1 and 8.0 in group 2 (ns).

During a trial of pancuronium-induced neuromuscular blockade, a close linear relation was found between the time to first detectable response to TOF nerve stimulation and the square root of PTC (Viby-Mogensen et al., 1981). This relationship can be expressed as:

$$t = a + b\sqrt{\text{PTC}}$$

where PTC is post-tetanic count, t is time from a given PTC to the first detectable TOF response, a is a constant (intercept) and b is the regression coefficient (slope).

Because of the rapid recovery rate of atracurium only two, or sometimes three, non-zero readings were obtained per patient in the present study. Therefore, each patient's regression coefficient could not be evaluated. Instead, for each group, all patient data were pooled and the optimal regression coefficient evaluated by the standard least squares method. As the objective of the PTC

TABLE I. *Age and weight distribution, and neuromuscular effect of atracurium 0.6 mg kg^{-1} in the two groups of patients. Group 1 = halothane* (n = 30)*; group 2 = fentanyl* (n = 30). *PTTS = Post-tetanic twitch stimulation; TOF = train-of-four nerve stimulation; PTC = post-tetanic count = number of responses to PTTS.* * *Statistically significant difference between groups* ($P < 0.05$)

	Group 1			Group 2		
	Mean	SD	Range	Mean	SD	Range
Age (yr)	33.4	12.9	18–76	35.4	11.7	18–60
Weight (kg)	63.5	12.7	42–88	69.0	13.4	44–99
Time (min) from injection to first response to:						
PTTS *	34.4	7.5	19–48	30.3	7.3	18–48
TOF	41.9	8.0	25–58	38.1	7.6	28–60
PTC at first response to TOF	7.6 (n = 11)	1.6	6–10	8.0 (n = 11)	2.0	4–11

method is to predict how soon after a given PTC the first detectable reaction to TOF will appear, and counts of 12 or more always occurred after the first response to TOF, these counts were excluded from the analysis.

The indices of regression are presented in table II. In both groups, there was a highly significant correlation between the square root of the PTC and the time-interval between a given PTC and the first detectable TOF response. Using standard methods, the estimated slopes of the two curves (*b*) were tested, but no significant difference was found. Using the pooled estimate of the slope (−4.9), the intercepts of the two curves (*a*) were then evaluated and tested. These intercepts, 14.1 for group 1 (halothane) and 13.2 for group 2 (fentanyl), were found to differ significantly. This implies that, throughout the PTC range of 1–12, the time before TOF for any given PTC was, on average, 1 min longer for the halothane group. However, this difference was not clinically significant. Therefore, both sets of data were combined and the overall curve (with 95% confidence intervals) is shown (fig. 1). The individual results have also been plotted to show the goodness-of-fit. It appears from figure 1 that a PTC of 1 indicates that the first detectable response to TOF would appear in, on average, 9 min, with 95% of the responses appearing between 4 and 14 min. The average time to first reaction to TOF corresponding to other PTC values can be read from the graph.

TABLE II. *Regression indices. SD = Standard deviation of the difference between observed and predicted values*

	Group 1	Group 2	Combined
a	14.8	12.5	13.7
b	−5.2	−4.5	−4.9
SD	2.42	2.05	2.29
Correlation coeff.	−0.848	−0.873	−0.85
Significance of correlation	$P<0.001$	$P<0.001$	$P<0.001$

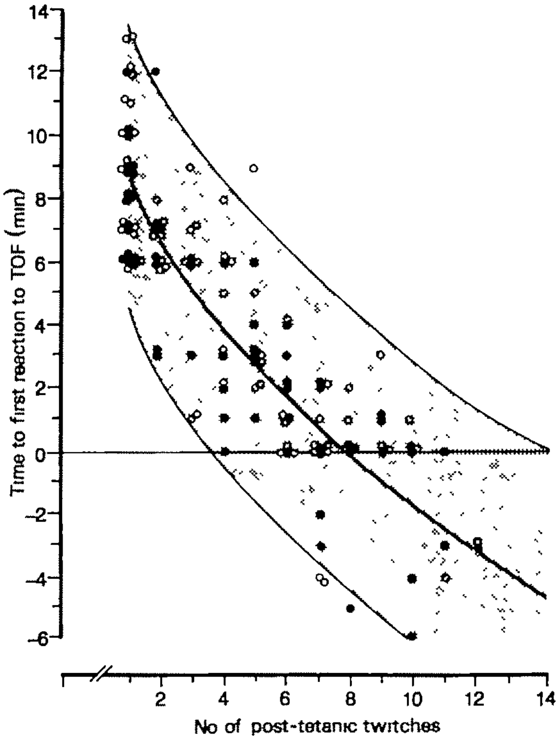

FIG. 1. Pooled data of 60 patients showing the relationship of post-tetanic count (PTC) and time of onset of TOF response. The predicted mean curve with 95% confidence limits are shown. ○ = Halothane group; ● = fentanyl group.

DISCUSSION

Our results indicate that, during intense neuromuscular blockade caused by atracurium, the PTC method gives early warning of the onset of neuromuscular recovery, offering the opportunity to maintain stable and smooth muscle relaxation.

The response to PTTS appeared, on average, 9 min (range 6–15 min) before the first detectable response to TOF stimulation. Further, a close correlation was found between PTC and the time-interval between the PTC and the first detectable response to TOF nerve stimulation (fig. 1). This implies that, even though a patient seems totally relaxed clinically, and no response to TOF or to single twitch stimulation can be elicited, it is still possible—using the PTC method—to evaluate the degree of blockade and, for instance, to decide when it will be necessary to give supplementary doses of atracurium. If there is no response at all to PTTS (PTC = 0), the blockade is still intense and it will take at least 8 min before the first response to TOF will appear. On the other hand, a PTC of, for instance, 6 or 7 would indicate that the first response to TOF is imminent (fig. 1).

The relationship between PTC and TOF found in this study differs from that present during neuromuscular blockade caused by pancuronium (Viby-Mogensen et al., 1981). Figure 2 shows the predicted mean curves (and 95% confidence limits) of the correlation between PTC and the time to first reaction to TOF for both pancu-

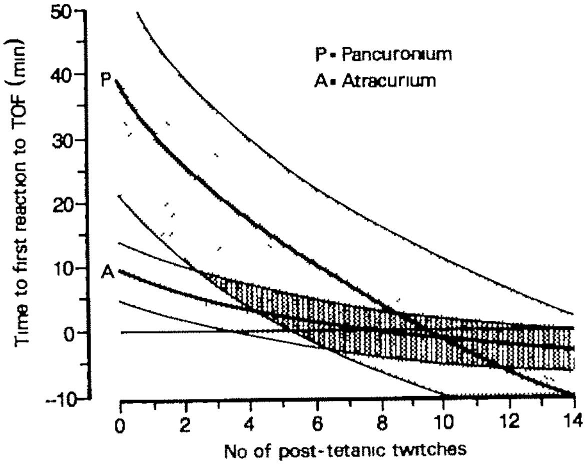

FIG. 2. Comparison of the relationship of post-tetanic count (PTC) and onset of TOF response for pancuronium (Viby-Mogensen et al., 1981) and atracurium. The predicted mean curves with 95% confidence limits are shown.

ronium (Viby-Mogensen et al., 1981) and atracurium. As would be expected, the slopes as well as the positions of the two curves differ. For example, during pancuronium-induced blockade a PTC of 2 indicates that the first TOF response will appear in 25 min. Contrary to this, during intense blockade caused by atracurium, a PTC of 2 would indicate that the first response to TOF would appear in, on average, 7 min. Therefore, whenever the PTC method is used to quantify intense non-depolarizing neuromuscular blockade, it is imperative to take into consideration the neuromuscular blocking drug used.

In summary, during intense atracurium-induced neuromuscular blockade, the time to the return of response to TOF stimulation may be derived from the PTC. It has previously been shown that the response to PTTS can be felt and counted (the PTC) with reasonable accuracy (Howardy-Hansen et al., 1984). In view of this, and the rapid recovery rate of atracurium, the PTC method appears to be a valuable supplement to TOF nerve stimulation during clinical anaesthesia involving atracurium.

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COMPLEMENT AND ANAPHYLATOXIN RESPONSES TO CROSS-CLAMPING OF THE AORTA

Studies During General Anaesthesia With or Without Extradural Blockade

A. BENGTSON, W. LANNSJÖ AND M. HEIDEMAN

SUMMARY

Complement activation and anaphylatoxin formation were studied in 28 patients undergoing aortic reconstructive surgery under general anaesthesia. In 12 of the patients an extradural catheter was placed in the L1–2 space and 2% mepivacaine was injected until blockade reached the T4 level. The remaining 16 patients were operated upon under general anaesthesia alone. Complement activation was not obvious until aortic cross-clamping. The release of anaphylatoxin was less pronounced during cross-clamping in the extradural group.

Clamping of the aorta during recontructive vascular surgery may produce alterations in haemodynamic and respiratory variables (Perry, 1968). Hypoperfusion, as indicated by altered acid–base status, and increases in lactate concentration and the plasma concentrations of purine metabolites, may occur (Schoenberg, Fredholm and Hohlbach, 1985). In addition, hypoperfusion and cross-clamping of the aorta are associated frequently with activation of the complement cascade and the formation of the anaphylatoxins C3a and C5a (Heideman and Bengtson, 1985). As the anaphylatoxins are potent mediators of smooth muscle contraction of arteries, trachea and airway preparations, and influence vascular permeability, significant circulatory and respiratory disturbances may occur as a result of the increase in anaphylatoxin activity (Hugli, 1979; Mahler et al., 1975; Pavek, Piper and Smedegård, 1979; Regal, Eastman and Pickering, 1980).

The neuroendocrine response to surgical stress and trauma includes increases in the plasma concentrations of the catecholamines, cortisol and free fatty acids (Carlsson and Liljedahl, 1963; Kehlet, 1982; Pflug, Halter and Tolas, 1982). Extradural analgesia provides a partial afferent neurogenic blockade that partially inhibits the endocrine-metabolic response to major surgery or trauma (Bromage, Shibata and Willougby, 1971; Engquist et al., 1977; Kehlet, 1982). It has been documented that extradural anaesthesia can modulate suppression of monocyte and lymphocyte functions during and after surgery (Walton, 1978; Hole and Unsgaard, 1983).

This investigation was designed to evaluate whether complement is activated during elective surgery for aortic occlusive disease and whether perioperative extradural blockade might influence anaphylatoxin formation during the period of aortic clamping.

PATIENTS AND METHODS

Patients

Twenty-eight patients were studied prospectively in association with elective surgery for aortic occlusive disease.

Premedication with pethidine and hyoscine i.m. was given 30 min before the scheduled time of surgery. All patients received a general anaesthetic technique which utilized 70% nitrous oxide in oxygen, fentanyl 0.002 mg/kg body weight, barbiturate (thiopentone 4 mg/kg body weight)

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TABLE I. *Characteristics of patients in the groups with and without extradural blockade. Mean values, standard errors of the mean and ranges*

	n	Age (yr)	M/F	Duration of operation (h)	Duration of clamping (h)	Perioperative blood loss (litre)
With blockade	12	66±4	9/3	4.5±0.7 (3.7–7.5)	1.3±0.2 (0.6–2.0)	1.5±0.6 (0.2–4.1)
Without blockade	16	68±3	11/5	4.8±0.6 (3.5–6.0)	1.3±0.3 (0.4–3.0)	1.3±0.3 (0.3–3.0)

and neuromuscular blockade (pancuronium 0.1 mg/kg body weight).

In 12 of the patients lumbar extradural blockade was provided in addition. A 22-gauge epidural catheter was placed in the L1–2 space with the aid of a Tuohy needle. Mepivacaine solution 2% was injected through the catheter until the block reached the T4 level. Additional mepivacaine (10 ml of 2% solution) was administered every 2 h throughout the operative procedure.

Methods

Arterial blood was obtained 5 min before aortic clamping, 5 min before the initial release of the cross-clamp restored the circulation to the first extremity, 5 min after the release of this clamp, and 5 min after the release of the second clamp.

Blood samples were immediately placed in tubes with EDTA (ethylene diamine tetra acetic acid 7.2 mg in 5 ml of blood) for plasma or without EDTA for serum. The tubes were centrifuged to remove the cells and the plasma or serum samples were kept at −80 °C until the complement activity, plasma concentrations of components C1 esterase inhibitor (C1 INH), C3, C4, C5, C3a and C5a were determined.

Whole complement (CH_{50}) was determined according to Mayer (1971). The complement components C1 INH, C3, C4 and C5 were determined with a rocket immunoelectrophoresis technique (Laurell, 1966). The plasma concentrations of C3a and C5a antigens were determined with a RIA-method (Wagner and Hugli, 1984). The concentrations of these components in our standard plasma did not differ from corresponding concentrations in a known reference plasma. All assays were carried out in duplicate with good correlation between the duplicate measurements.

Statistics

Mean values and standard errors of the mean are presented. Fisher's test was used for comparison of groups and correlation studies (Bradley, 1968). Differences were described as significant when $P < 0.05$. The least squares linear regression test was used for correlation studies (Colton, 1974).

RESULTS

Age, duration of operation, duration of aortic clamping and blood loss were similar in both groups (table I).

Whole complement values (CH_{50}) in all patients are given in table II. Whole complement activity decreased during the period of aortic clamping in the patients studied ($P < 0.05$). This reduction was, however, less pronounced in the extradural group ($P < 0.05$).

Plasma C1 INH, C4, C3 and C5 decreased in both groups during surgery ($P < 0.05$). However, these variables remained within their normal ranges even after cross-clamping of the aorta. The decreases in these components did not differ significantly in the two groups studied.

Simultaneously, the plasma concentrations of C3a increased (fig. 1) in both groups (extradural group $P < 0.05$; non-extradural group

TABLE II. *Whole complement activity (CH_{50}) in 28 patients during surgery. Mean values and standard errors of the mean*

	CH_{50} (u. ml^{-1})
Normal value	92
Range	(82–112)
With extradural blockade (n = 12)	
5 min before aortic clamp	91±4
5 min before clamp release	78±5
5 min after release of first clamp	77±5
5 min after release of second clamp	76±4
Without extradural blockade (n = 16)	
5 min before aortic clamp	88±4
5 min before clamp release	71±6
5 min after release of first clamp	69±4
5 min after release of second clamp	67±5

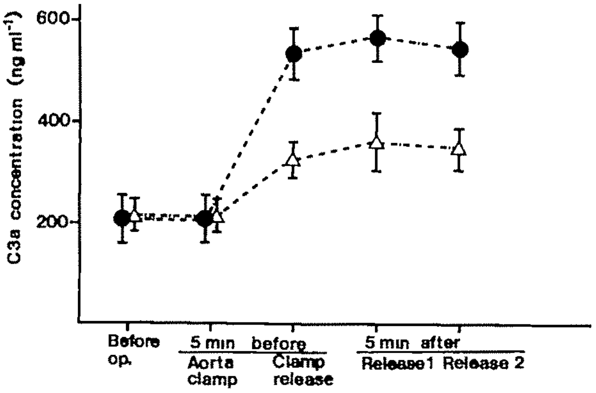

FIG. 1. The increase in plasma C3a concentration during cross-clamping in patients with (△) and without (●) extradural blockade. ($P < 0.001$.)

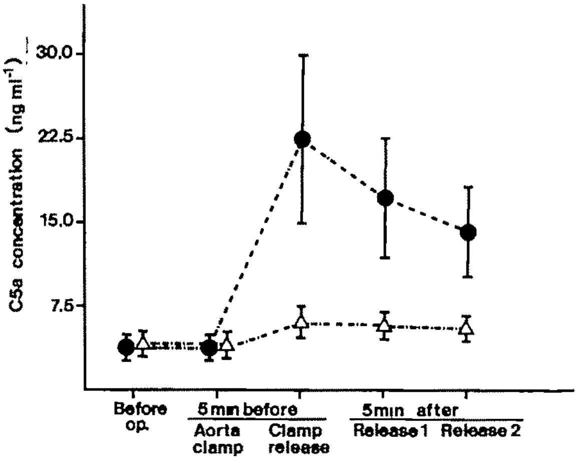

FIG. 2. The increase in plasma C5a concentrations in patients with (△) and without (●) extradural blockade. ($P < 0.05$.)

$P < 0.001$). However, the plasma C3a concentration increased more in patients who did not receive the extradural block compared with those who did ($P < 0.001$). Similar changes in plasma concentrations of C5a were also seen during aortic clamping. Plasma C5a concentration increased during the period of aortic clamping (fig. 2) in patients with and without extradural blockade ($P < 0.05$ and $P < 0.01$, respectively). C5a concentrations increased more in the group without extradural block ($P < 0.05$).

Duration of clamping correlated with the increase in plasma C3a concentration ($r = 0.64$, $n = 16$, $P < 0.05$) in patients without extradural block. This positive correlation was not observed ($r = 0.16$, $n = 12$) in the extradural group (fig. 3).

Frequency of postoperative complications such as infection, bacteraemia and ARDS did not differ between the two groups. One patient in each group developed multisystem organ failure with pulmonary, renal and hepatic insufficiency in the postoperative period.

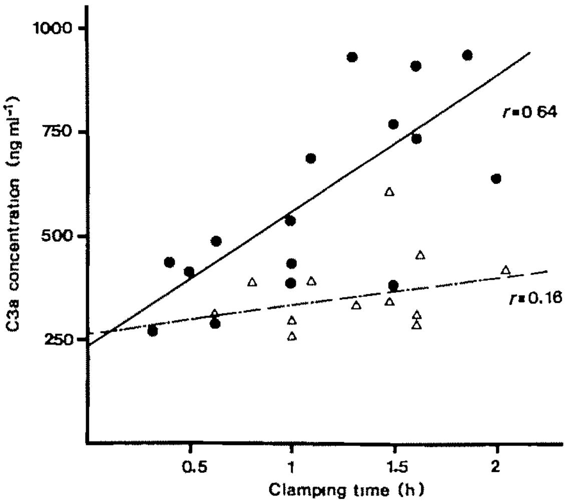

FIG. 3. The correlation between duration of cross-clamping and plasma C3a concentration in patients with (△) ($r = 0.16$) and without (●) ($r = 0.64$) extradural block. ($P < 0.05$.)

DISCUSSION

This study indicates that the complement cascade is activated during reconstructive surgery for aortic occlusive disease. The complement variables measured were similar in both groups before the clamping of the aorta. The activation occurs primarily during aortic clamping and is detected by a decrease in whole complement activity and an increase in plasma anaphylatoxin concentrations. CH_{50} titres indicate the absolute activity and C3a concentrations indicate the plasma range of active and non-active C3a. This might be one reason why CH_{50} titres decreased by about 20% while C3a increased by around 270%. Increases in pulmonary artery pressure and pulmonary vascular resistance are often found in patients undergoing surgery for aortic aneurysm or aortic occlusive disease (Lunn, Dannemiller and Stanley, 1979). These haemodynamic changes might be partly explained by the increases in anaphylatoxin activity, as C3a and C5a increase vascular tone (Marceau and Hugli, 1984). During extradural blockade, the degree of complement activation during operation was less pronounced when compared with general anaesthesia alone.

Similarly, the formation of the anaphylatoxins increased only slightly in the extradural group.

Perioperative extradural blockade might be beneficial in regard to the incidence of peri- and postoperative complications although, in this study, we were unable to find any correlation with the incidence of postoperative infection, wound healing and multi-system organ failure. However, the groups studied were too small, and the trauma possibly insufficiently extensive, to reveal clinically observed changes in a multifactorial disease with a relative low incidence.

The mechanisms behind the effects of extradural blockade on complement activation and anaphylatoxin release are not fully understood. The influence of local anaesthetics on biological structures and living cells have been documented (Papahadjopoulos et al., 1975; Feinstein et al., 1977). In addition, inhibition of human leucocyte metabolism and random mobility by lignocaine has been reported (Hammer, Dahlgren and Stendahl, 1985). These responses are mediated by several factors, including the complement cascade. Membrane stabilization by local anaesthetics is one possible mechanism by which the complement cascade, and the formation of biologically active split products, might be influenced. Afferent inhibition by extradural blockade might be another mechanism influencing the activation of complement.

Recent evidence indicates that anaphylatoxins stimulate biosynthesis of the arachidonic acid products, leucotrienes and prostaglandins (Stimler et al., 1982). Prostaglandin production has been reported in association with altered pulmonary function and central haemodynamics (Cooper et al., 1980).

As anaphylatoxins are potent mediators of histamine, leucotrienes, prostaglandins, thromboxane and the platelet-activating factor, they might account for clinical effects observed when increased concentrations of C3a and C5a appear in plasma (Goldstein et al., 1973; Habal, Movat and Burrowes, 1974; Kaplan, 1978; Bokisch and Muller-Eberhard, 1979; Ghebrehiwet, Silverberg and Kaplan, 1981). C5a is inactivated by circulating carboxypeptidase, which cleaves one arginine residue off the N-terminal end, producing C5a desArg (Bokisch and Muller-Eberhard, 1979). C5a and C5a desArg are bound avidly to neutrophils, where they are internalized and degraded (Chenoweth and Hugli, 1978, 1980). A rapid elimination pattern could, in fact, mask the increased formation of C5a. The leucocyte count was, however, never extremely low in either of the groups studied.

The correlation between duration of clamping and the increase in anaphylatoxin concentration fits well with the clinical impression that a long-standing occlusion of a major artery is associated with increased risk of haemodynamic complications. Other investigators have also found increases in anaphylatoxin concentrations in association with aortic surgery. They have suggested that an anaphylactic reaction against the aortic prosthesis could cause the release of the anaphylatoxin (Shepard et al., 1984; Roizen et al., 1985). Although different synthetic vascular prosthesis materials are able to induce anaphylatoxin release, the aortic cross-clamping itself is one reason for complement activation as the anaphylatoxins increase during clamping before the graft has been inserted.

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ACUTE VENTILATORY CHANGES DURING I.V. INDUCTION OF ANAESTHESIA WITH THIOPENTONE OR PROPOFOL IN MAN

Studies Using Inductance Plethysmography

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Propofol (2,6 di-isopropylphenol formulated as an emulsion) has been shown to be a suitable agent with which to induce anaesthesia for short procedures and day case surgery (Cummings et al., 1984; Cummings and Spence, 1985; Redfern et al., 1985). However, a number of studies have shown that the administration of propofol is associated with respiratory depression characterised by periods of apnoea (Goodman, Carter and Black, 1985; Taylor et al., 1987). Interest lies in whether the mechanism of this respiratory depression is central in nature, as with opioid drugs which depress respiration by producing apnoea (Prys-Roberts and Kelman, 1967) or more peripheral in nature, as with drugs such as thiopentone (Jordan, 1982).

In an attempt to investigate the mechanism of the respiratory depression, we have compared the changes in ventilation during the induction of anaesthesia in two similar groups of patients, using ventilatory inductance plethysmography (VIP) (Respitrace Ambulatory Monitoring Systems Inc., New York). The use of VIP for the study of the respiratory effects of drugs has been described previously (Jordan, Jones and Pinto, 1979; Catling et al., 1980) and has the advantage that changes in resting lung volume can be recorded as well as changes in ventilation and the pattern of breathing.

SUMMARY

We have compared the acute ventilatory changes during induction of anaesthesia with equipotent doses of thiopentone and propofol in 12 premedicated female patients. Using ventilatory inductance plethysmography we have shown that both agents depress respiration to a similar and significant degree ($P < 0.001$)*. However, although the functional residual capacity was reduced in patients receiving propofol, it increased slightly after induction with thiopentone* ($P < 0.05$)*.*

PATIENTS AND METHODS

Twelve female patients (ASA Grade I) about to undergo elective minor gynaecological surgery were studied. All patients gave their written informed consent to inclusion in the trial, which had been approved by the hospitals ethics committee.

All patients received papaveretum and hyoscine as premedication which was given i.m. approximately 1 h before the induction of anaesthesia (< 50 kg: papaveretum 10 mg, hyoscine 0.2 mg; 50–70 kg: papaveretum 15 mg, hyoscine 0.3 mg; > 70 kg: papaveretum 20 mg, hyoscine 0.4 mg). Anaesthesia was induced with either thiopentone 4 mg kg^{-1} or propofol 2.5 mg kg^{-1}. These doses have been shown to be equipotent (Grounds, Moore and Morgan, 1986).

Minute ventilation ($\dot{V}_{\mathrm{E}}$) and its subdivisions (tidal volume (V_{T}), frequency (f), the time of inspiration (T_{I}) and expiration (T_{E}), the duty inspiratory cycle ($T_{\mathrm{I}}/T^{\mathrm{tot}}$, where $T^{\mathrm{tot}} = T_{\mathrm{I}} + T_{\mathrm{E}}$)

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and mean inspiratory flow (V_T/T_I)) were monitored with an inductance plethysmograph (VIP). Briefly, this consists of two elasticated bands containing coils of wire placed around the chest and abdomen. Movement of the chest wall and abdomen causes changes in the self inductance of the coil of wire which can be processed subsequently to produce a volume signal. Additionally, when the inductance plethysmograph is used in its d.c. mode, overall changes in lung volume (for example with changes in functional residual capacity (FRC)) also cause corresponding changes in self inductance, so that such changes can be estimated. At least 90 min before the start of any recordings, the VIP belts were attached to the thorax and abdomen of the patients to allow the belts to achieve thermal equilibrium.

Before induction, the inductance plethysmograph was calibrated against a spirometer using a single posture technique (Mannix et al., 1984) and compared with the tidal volumes obtained from simultaneous water-bell spirometry (for 20 breaths). The validation confirmed the accuracy of the plethysmograph and provided a tidal volume ratio (spirometer:plethysmograph) with which volume measurements could be corrected subsequently. Analysis of data from the inductance plethysmograph was carried out on-line by a microcomputer and used to display a breath-by-breath update of ventilation and its subdivisions on a monitor. In addition, all variables were recorded continuously on a chart recorder. Changes in FRC during induction were estimated from changes in the end-expiratory lung volume. Mean values of minute ventilation, its subdivisions, and of the end-expiratory volume were obtained for 1-min time periods starting 1 min before the beginning of the induction of anaesthesia and ending 3 min after induction. Changes in the FRC during induction were estimated by calculating the change in end-expiratory volume from that obtained just before induction.

On the patient's arrival in the anaesthetic room, an ECG was attached to the patient and an i.v. cannula inserted (under local analgesia) to a suitable forearm vein. A pulse oximeter was attached to one earlobe of each patient (Ohmeda Biox III).

Before the induction of anaesthesia, the patients were asked to breathe 100% oxygen via a Magill anaesthetic breathing system for at least 3 min. Anaesthesia was induced using the equipotent doses of either thiopentone 4 mg kg^{-1} or propofol 2.5 mg kg^{-1} given over 30 s (by R.M.G.). The investigator making the VIP recordings (D.M.) was unaware of the induction agent which the patient received.

If any patient's airway became obstructed during the period of measurement, this obstruction was relieved by the supervising anaesthetist (M.B.T.) and that patient excluded from the trial. If apnoea occurred, ventilation was assisted only if the oxygen saturation measured by the pulse oximeter decreased to less than 90%; the patient was then excluded from the study. Although three patients were apnoeic for longer than 20 s, the measured oxygen saturation did not decrease to less than 90%; thus no patient required assisted ventilation.

The study was considered complete when either 4 min had elapsed from the start of the i.v. injection or the patient showed clinical signs of starting to waken. The patient was then given a further suitable dose of the initial i.v. induction agent and anaesthesia was continued using a suitable conventional general anaesthetic technique.

The statistical analysis was by analysis of variance, and Student's *t* test where appropriate.

RESULTS

The demographic details of the patients studied are shown in table I. All patients were female. There were no significant differences between the groups for age, weight or height. The numbers of patients remaining apnoeic for longer than 20 s were: one patient in the thiopentone group (47 s) and two patients in the propofol group (21 and 52 s).

Table II shows the changes in ventilatory variables recorded by VIP. Changes in FRC are recorded as changes from baseline, where baseline was the mean value during the 1 min before induction.

TABLE I. *Demographic details of patients studied*

	Thiopentone	Propofol
No. patients	6	6
Age (yr) (mean ± SEM)	34.1 ± 3.5	36.0 ± 5.6
Range (yr)	26–48	22–52
Weight (kg) (mean ± SEM)	66.2 ± 4.63	64.21 ± 3.75
Range (kg)	48.5–83.5	57.0–81.5
Height (m) (mean ± SEM)	1.67 ± 0.34	1.65 ± 0.41
Range (m)	1.55–1.80	1.50–1.80

TABLE II. *Changes (mean ± SD) in minute volume, frequency of ventilation* (f), *tidal volume* (V_T) *mean inspiratory flow rate* (V_T/T_I), *the duty inspiratory cycle* (T_I/T^{tot}) *and change in function residual capacity* (δ*FRC*) *during induction of anaesthesia with either thiopentone or propofol. Significant effect of time (but not drug) on:* V_T ($P < 0.001$); V_T/T_I ($P < 0.05$); $\dot{V}_E$ ($P < 0.01$). *Significant interaction between drug and time for: FRC* ($P < 0.05$)

	Drug	Time (min)			
		−1–0	0–1	1–2	2–3
$\dot{V}_E$ (litre min^{-1})	Thiopentone	5.28(1.7)	4.73(2.1)	3.62(1.9)	3.88(1.1)
	Propofol	5.72(1.6)	5.78(2.3)	3.30(1.8)	4.87(2.5)
f(b.p.m.)	Thiopentone	17.6(8.4)	16.1(7.9)	13.9(7.7)	16.3(6.4)
	Propofol	16.2(5.5)	14.4(5.5)	13.7(10.4)	15.5(6.5)
V_T (ml)	Thiopentone	325(121)	288(110)	239(100)	254(133)
	Propofol	378(185)	449(212)	229(200)	306(200)
V_T/T_I (litre min^{-1})	Thiopentone	11.9(3.4)	11.5(5.2)	9.2(4.7)	9.5(2.9)
	Propofol	13.0(3.8)	14.4(7.9)	10.0(4.7)	13.5(6.1)
T_I/T^{tot}	Thiopentone	0.444(0.05)	0.420(0.08)	0.410(0.1)	0.431(0.12)
	Propofol	0.445(0.07)	0.385(0.11)	0.331(0.13)	0.366(0.08)
δFRC (ml)	Thiopentone	0	69(140)	59(197)	104(204)
	Propofol	0	−122(202)	−228(241)	−205(236)

Analysis of variance revealed significant decreases in minute ventilation ($P < 0.01$), tidal volume ($P < 0.001$) and mean inspiratory flow ($P < 0.05$) following induction with both agents. These decreases were always maximal between the 1st and 2nd minutes after the start of induction. These decreases were all significant with respect to time, but not to the drug used for induction. In the patients given propofol, tidal volume decreased at a later stage and the mean inspiratory flow recovered earlier than in the thiopentone group. Although, in both groups, induction was accompanied by a reduction in ventilatory frequency, this was small and not statistically significant. However, overall there were no statistically significant differences in the pattern of breathing between the groups.

Changes in FRC during induction have been displayed as changes from baseline. From these data, it can be seen that there was a slight increase (59–104 ml) in FRC in the thiopentone group in the 3 min following induction, but a reduction of 122–228 ml in FRC in the propofol group during the same period. The difference between the two groups during this period was significant ($P < 0.05$).

The contribution of abdominal movement to each tidal volume, and the degree of paradoxical movement, were also measured with the inductance plethysmograph. Although there were no differences in the contribution from the abdominal belt between the two patient groups, and there was a trend towards an increase in paradoxical movement with the onset of anaesthesia, none of the changes was statistically significant.

DISCUSSION

This study confirms previous work (Bellman and Pleuvry, 1981; Taylor et al., 1986) that propofol is a respiratory depressant and that, in equipotent anaesthetic doses, it is as potent a respiratory depressant as thiopentone. However, it should be appreciated that in the study by Grounds, Moore and Morgan (1986) of the equipotency of propofol and thiopentone, the patients were not premedicated with an opioid—as in this study. The depression of minute volume produced by equipotent doses of the two agents was similar, but unlike the study in rabbits by Bellman and Pleuvry (1981), we did not find that the depression of minute volume produced by thiopentone was almost solely as a result of depression of ventilatory frequency. The depression of minute volume with both agents was caused by a reduction in both tidal volume and ventilatory rate, confirming the earlier work of Taylor and colleagues (1986) in which ventilation was monitored using a pneumotachograph. Despite having an opioid premedication, neither group of patients exhibited an opioid type of ventilatory depression, in which tidal volume may be increased but ventilatory rate reduced (Smith et al., 1967; Hunter, Pleuvry and Rees, 1968).

In this study, we have used a non-invasive method (VIP) to monitor the changes in ventilatory pattern during the induction of anaesthesia. Changes in ventilation or the pattern of breathing may result from alterations in V_T/T_I or T_I/T^{tot} ($V_E = V_T/T_I \times T_I/T^{tot}$). In normal subjects, V_T/T_I may be taken as a reasonable reflection of central neuromuscular ventilatory drive and T_I/T^{tot} reflects the action of the central timing mechanism (Derenne et al., 1976). Our results suggest that the ventilatory depression accompanying the induction of anaesthesia is caused by a decrease in central inspiratory drive rather than a change in central timing. When allied to the reports of an increased frequency of apnoea following propofol (McCollum, Dundee and Robinson, 1986, unpublished observations; Taylor et al., 1986), these data suggest that the mechanism of the apnoea is dissimilar to that of the opioid drugs (Prys-Robert and Kelman, 1967) when a decrease in the ratio T_I/T^{tot} would have been anticipated. However, during the present study we examined changes during the peri-induction period. This time period was chosen because the equipotent induction doses for sleep between the two agents have been defined (Grounds, Moore and Morgan, 1986). A further study comparing the two agents during steady state infusions for anaesthesia may produce different conclusions. However, these equipotent steady state infusion rates for anaesthesia are unknown.

In this study, the FRC decreased in the patients who received propofol. This was an entirely expected change and is in accordance with previous work on other i.v. and volatile anaesthetic agents (Hewlett et al., 1974). However, in addition we have shown a slight increase in FRC in the first 3 min following i.v. induction of anaesthesia with thiopentone. This result was unexpected and would be very difficult to validate using conventional steady state helium dilution techniques for the measurement of FRC. Don, Wahba and Craig (1972) felt that the primary change in ventilatory mechanics during anaesthesia was "probably a mechanical phenomenon associated with an alteration of the position of the chest wall," but this would not explain our findings of a small increase in FRC immediately after induction with thiopentone.

In conclusion, although propofol 2.5 mg kg^{-1} may be a relatively large dose for induction of anaesthesia in patients who are premedicated, it is interesting to note that this appears to be no more depressant than an equipotent dose of thiopentone. However, there are reports of a higher frequency of apnoea following induction with propofol (McCollum, Dundee and Robinson, 1986, unpublished observations; Taylor et al., 1986), and this may provide an additional problem when propofol is used in a single dose technique for the induction and maintenance of anaesthesia for short procedures and day case surgery. However, ventilatory depression may confer some benefits when propofol is used, by continuous infusion, to provide sedation in patients requiring long term intermittent positive pressure ventilation in the intensive care unit. It would allow for easier and, therefore, better management of this group of patients.

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PHARMACOKINETICS OF PROPOFOL IN FEMALE PATIENTS

Studies Using Single Bolus Injections

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SUMMARY

The pharmacokinetics of propofol in a dose of 2.5 mg kg^{-1} given via a vein in the antecubital fossa were studied in 18 patients. Anaesthesia was maintained with nitrous oxide in oxygen in all patients. The effects of pretreatment with fentanyl (n = 6) and maintenance with halothane (n = 6) on the pharmacokinetics of propofol were also investigated. Pretreatment with fentanyl resulted in prolonged apnoea in four patients. No serious side effects occurred. The pharmacokinetics of propofol in unpretreated patients who were maintained with nitrous oxide in oxygen only can be described by a three-compartment open mammalian model with very rapid distribution ($T_{\frac{1}{2}}^{\alpha}$ about 3 min), rapid elimination ($T_{\frac{1}{2}}^{\beta}$ 45 min) and a slower final phase ($T_{\frac{1}{2}}^{\gamma}$ about 300 min). The total body clearance of propofol was rapid (1.91 litre min^{-1}). Propofol was initially distributed into a relatively large central compartment (41.3 litre) and was extensively redistributed (V^{ss} 305 litre; V^{γ} 722 litre). Throughout the sampling period the mean blood concentrations of propofol for the patients pretreated with fentanyl were about 50% higher than the mean concentrations for patients maintained with nitrous oxide only. Mean propofol concentrations for the patients maintained with halothane were intermediate between those of the other two groups.

Initially, propofol (2,6-di-isopropylphenol), was formulated in Cremophor EL and was found to induce anaesthesia smoothly in patients when given by i.v. injection (Briggs et al., 1981). Induction doses ranged from 1 to 4 mg kg^{-1} and were administered over 20–30 s into a peripheral vein. Success of induction was affected by dose and the use of premedication (Briggs, Bahar et al., 1982). The drug was distributed rapidly in the body and had a short elimination half-life as a result of rapid metabolism (Adam et al., 1983).

In view of the concern about the Cremophor vehicle with respect to potential anaphylactoid reactions (Clarke et al., 1975), propofol was re-formulated in an aqueous oil-in-water emulsion (Diprivan, ICI plc). When given i.v. to animals, the emulsion formulation also induced anaesthesia, the dose requirements and anaesthetic properties being similar to those seen with the Cremophor formulation (Glen and Hunter, 1984).

Using the emulsion formulation of propofol, an initial study to determine the generally effective induction dose was carried out in 115 unpremedicated patients (Cummings et al., 1984). Anaesthesia was induced in 87% of the patients given propofol at 2.0 mg kg^{-1} and in 95% of the patients given 2.5 mg kg^{-1}.

In the present open study the pharmacokinetics of propofol (as the emulsion) have been evaluated in patients given an induction dose of 2.5 mg kg^{-1}. Anaesthesia was maintained with nitrous oxide in oxygen.

In an earlier study (Prys-Roberts, personal communication) with the Cremophor formulation, patients who received a bolus dose of fentanyl 5 μg kg^{-1} at the time of induction with propofol 1.5 mg kg^{-1} and before the start of a zero order infusion of propofol 0.05 mg kg^{-1} min^{-1} took significantly longer to open their eyes ($P < 0.001$),

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and had significantly higher blood concentrations ($P < 0.005$) than patients in whom a similar procedure was followed without pretreatment with fentanyl. In this present study, therefore, the effects of pretreatment with fentanyl on the pharmacokinetics of propofol have been studied, together with the clinical features of this anaesthetic–analgesic combination. Similarly, the effect of supplementing the nitrous oxide in oxygen with halothane has been investigated.

PATIENTS AND METHODS

Following approval by the Hospital Ethical Committee, informed consent was obtained from 18 healthy (ASA grade I), unpremedicated Caucasian female patients about to undergo minor gynaecological procedures. Demographic data are summarized in table I.

Patients were excluded if they had hepatic, renal, haematological, metabolic or cardiovascular disease, were grossly obese, if they were receiving any drug therapy known to affect liver function or hepatic blood flow, or if they had previous adverse experience of general anaesthesia.

Patients were assigned to one of three groups of six patients; it was not possible to randomize this allocation because of clinical considerations. No premedication was given. The groups received the following:

(a) Propofol 2.5 mg kg^{-1} to induce anaesthesia; maintenance with nitrous oxide in oxygen (2:1) only. (Control group.)

(b) Pretreatment with fentanyl 100 µg i.v. 5 min before induction with propofol 2.5 mg kg^{-1} and maintenance with nitrous oxide in oxygen (2:1) only. (Fentanyl group.)

(c) Propofol 2.5 mg kg^{-1} (to induce anaesthesia) and maintenance with halothane (initially 3% then reducing to 1.5%) together with nitrous oxide in oxygen (2:1). (Halothane group.)

The induction dose of propofol was given in all groups, over a period of 20 s, into a large vein in the antecubital fossa via a 16-gauge cannula. Arterial pressure and heart rate were measured before, and every minute during surgery (Dinamap), and the patients were observed for evidence of ventilatory depression.

Induction time was measured from the start of injection using the loss of count measurement. Any side effects at induction were noted and any pain on injection was recorded. On completion of surgery, inhalation anaesthetics were discontinued and the times at which each patient opened her eyes on command and gave her correct date of birth were recorded. Any venous sequelae were noted.

Blood samples were obtained via a 16-gauge cannula which had been inserted to a large vein in the contralateral antecubital fossa under local anaesthesia. The cannula was kept free flowing and flushed with heparinized saline, as required. The deadspace was removed before sampling, which was carried out before and at 2, 4, 6, 8, 10, 15, 30, 45, 60, 90, 120, 150, 180, 240, 300, 360, 420 and 480 min after the end of the administration of propofol. The samples were thoroughly mixed in tubes containing potassium oxalate, and stored at +4 °C whilst awaiting analysis. The propofol concentration in blood samples was determined by a modification of the method described by Adam and colleagues (1981). The cyclohexane extract was basified with tetramethyl ammonium hydroxide and evaporated to dryness under nitrogen. After reconstitution, the residue was subjected to high pressure liquid chromatography with fluorescence detection. This method has a limit of quantification of approximately 2 ng ml^{-1} and the inter-batch coefficient of variation of the assay over the concentration range observed in this study was approximately 8%. Pharmacokinetic analysis of each data set was performed using the extended least squares curve fitting program "Elsfit" (Peck et al., 1984), initial parameter estimates having been derived using the standard feathering technique. The choice of pharmacokinetic model was made on the basis of the Schwarz criterion (Schwarz, 1978) together with an assessment of the residuals of the data from the line of best fit. The Schwarz criterion gave an objective statistical assessment of the advantages, if any, of the additional exponential function when comparing, in this case, a three-compartment with a two-compartment model. The statistical significance of differences between treatment groups in recovery times, propofol blood concentrations and derived pharmacokinetic parameters was assessed using the Student's *t* test.

TABLE I. *Demographic data (mean values ± SD)*

	Control group	Fentanyl group	Halothane group
Age (yr)	34.8±8.6	39.3±11.5	38.2±7.4
Weight (kg)	57.5±4.4	58.5±10.4	58.5±8.2

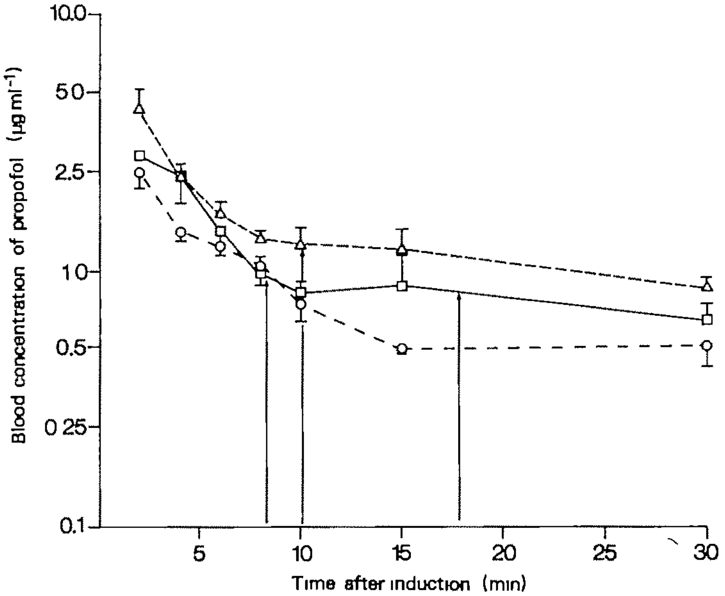

FIG. 1. Mean ($\pm$SEM, $n = 6$) blood concentrations of propofol up to 30 min after induction with propofol 2.5 mg kg^{-1} and mean recovery times (↑ = eyes open on command) for the fentanyl–nitrous oxide (△), halothane–nitrous oxide (□) and nitrous oxide only (○) subgroups.

RESULTS

Anaesthesia was induced successfully in all patients with a mean induction time of 27.1 ± 7.0 (SD) s. One patient had the injection given in the dorsum of her hand, as no other suitable vein could be found.

One patient in the halothane group had some excitatory movements at induction, and one patient in the control group reported tingling of the face and coldness of her throat. These inductions were recorded as adequate; all others were recorded as good. There was no case of pain on injection, but one patient noted some tingling in the antecubital fossa.

Apnoea (ranging in duration from 60 to 450 s) occurred in four patients who had received fentanyl; these patients were manually ventilated with nitrous oxide in oxygen (2 : 1) via a face mask. The maintenance of anaesthesia was uneventful except for three patients in the halothane group in whom there were spontaneous movements; these were adjudged to be attributable to light anaesthesia.

Postoperative complications, none serious, were observed in three patients (one from each group). These were: one case of nausea, one of headache and one of vomiting, cough and laryngospasm. In the remaining patients recovery was excellent. No venous sequelae were seen immediately after operation or in the 13 patients who were inspected at 24 h.

The mean duration of the operative procedure in the fentanyl group (6.6 min) was similar to that for the control group (5.9 min) whilst that for the halothane group (11.3 min) was much longer. The mean time to eyes open after discontinuation of inhalation anaesthesia (recovery time) was approximately 50% longer for the fentanyl group (3.5 min) than for the nitrous oxide only group (2.3 min); however, this difference was not statistically significant. Recovery time for the halothane group (6.5 min) was significantly ($P < 0.05$) longer than those for both other treatment groups. No accurate estimate of the propofol concentration on awakening could be made for all individuals because of the erratic shapes of the propofol blood profiles during this period. However, the mean propofol concentrations at the mean waking time for each treatment group were approximately 1 μg ml^{-1}.

Mean propofol blood concentration profiles for the three treatment groups are displayed in figure 1, for time points up to 30 min, and in figure 2, for time points up to 8 h.

Propofol blood concentrations in all patients declined rapidly for approximately 10 min following the end of dosing; in about one-half of the

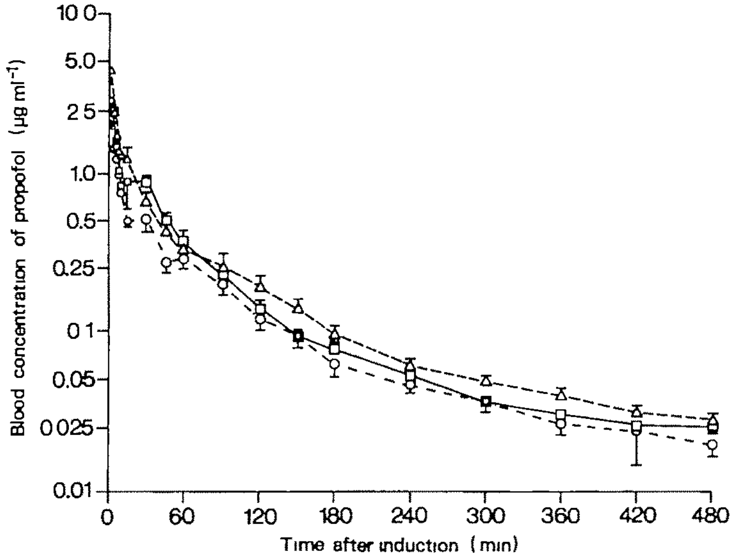

FIG. 2. Mean (±SEM, $n = 6$) blood concentrations of propofol up to 8 h after induction with propofol 2.5 mg kg⁻¹ for the fentanyl–nitrous oxide (△), halothane–nitrous oxide (□) and nitrous oxide only (○) subgroups.

patients this smooth decline continued. In the remainder, the propofol concentrations showed an increase, in one patient reaching, at 15 min, the concentration recorded at 2 min (fig. 3). In these latter patients, the wide scatter of data about any smooth fitted curve, in the period up to 30 min after the dose, reduced the confidence of estimates of the pharmacokinetic parameters associated with the first exponential phase.

Observed secondary peaks in the propofol blood concentration profiles all occurred after the end of surgery and after the termination of gaseous anaesthesia; these peaks were observed in at least two patients in each treatment group.

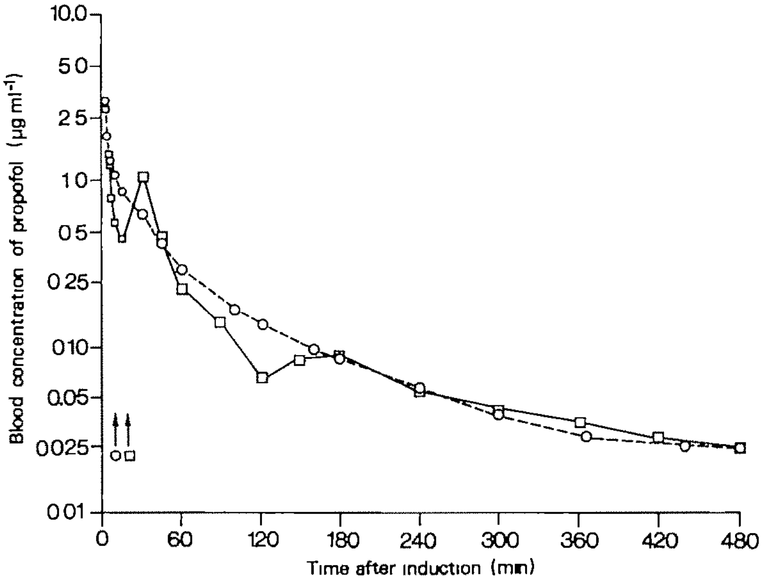

FIG. 3. Individual profiles of blood concentrations of propofol showing a smooth decline (○---○) and a secondary peak (□——□) together with their corresponding recovery times (↑ = eyes open on command).

TABLE II. *Mean propofol pharmacokinetic parameters* (± *SEM*). †n = *4*; ‡n = *5*

	Control group (n = 6)	Fentanyl group (n = 6)	Halothane group (n = 6)
A (μg ml^{-1})	5.10 ± 1.77	10.7 ± 4.7	6.10 ± 2.79
α (min^{-1})	0.384 ± 0.135	0.702 ± 0.197	0.441 ± 0.112
$T_{\frac{1}{2}}^{\alpha}$ (min)	2.85 ± 0.72	1.80 ± 0.64	4.09 ± 2.56
B (μg ml^{-1})	0.605 ± 0.068	1.14 ± 0.19	1.08 ± 0.11
β (min^{-1})	0.0167 ± 0.0023	0.0264 ± 0.0060	0.0236 ± 0.0035
$T_{\frac{1}{2}}^{\beta}$ (min)	45.0 ± 5.1	34.0 ± 7.9	33.6 ± 5.8
C (μg ml^{-1})	0.0698 ± 0.0052†	0.145 ± 0.030‡	0.137 ± 0.016†
γ (min^{-1})	0.00261 ± 0.00040†	0.00357 ± 0.00043‡	0.00386 ± 0.00035†
$T_{\frac{1}{2}}^{\gamma}$ (min)	284 ± 40†	208 ± 30‡	184 ± 15†
AUC∞ (μg min ml^{-1})	81.6 ± 11.4†	108 ± 8‡	85.4 ± 9.7†
V (litre)	41.3 ± 13.0†	21.8 ± 6.7‡	34.5 ± 9.1†
V^{γ} (litre)	722 ± 34†	387 ± 59‡	460 ± 57†
(litre kg^{-1})	12.6 ± 0.4†	7.00 ± 0.83‡	7.96 ± 0.86†
V^{ss} (litre)	305 ± 30†	171 ± 28‡	229 ± 40†
(litre kg^{-1})	5.31 ± 0.46†	3.11 ± 0.46‡	3.91 ± 0.59†
Total body clearance			
(litre min^{-1})	1.91 ± 0.37†	1.29 ± 0.05	1.79 ± 0.27†
(ml min^{-1} kg^{-1})	32.9 ± 5.6†	23.7 ± 1.7‡	30.4 ± 3.2†

The blood concentration of propofol (C_t) at any time (t) after administration was best fitted for the patients in this study by a triexponential equation of the form:

$$C_t = Ae^{-\alpha t} + Be^{-\beta t} + Ce^{-\gamma t}$$

where A, B and C are the intercepts and α, β and γ the slopes of the three exponential phases.

The data were, therefore, treated as conforming to a three-compartment open mammalian model with elimination from the central compartment, and the relevant pharmacokinetic parameters were calculated for each individual data set. Mean data for each treatment group are presented in table II.

For five out of 18 patients there were insufficient propofol concentration data to define with adequate confidence the parameters of the third exponential phase; for these individuals the fitted values for the first two phases only have been reported and no estimates have been made of the area under the propofol concentration–time curve extrapolated to infinity (AUC$_{\infty}$), the derived total body clearance or the apparent volumes of distribution.

For the control group, propofol blood concentrations declined over the first 15 min after induction with a mean half-life of 2.85 min; over the following 2–3 h concentrations declined more slowly with a mean half-life of 45 min, whilst the final observed phase mean half-life was 284 min.

The central compartment volume showed wide interindividual variability (mean 41.3 ± 13.0 (SEM) litre; range 11.7–99.9 litre), but all individual values were much greater than blood volume. The mean apparent volume of distribution at distribution equilibrium (V^{γ}) was very large (722 litre; range 635–796 litre, 11.5–13.3 litre kg^{-1}), as was the mean volume of distribution at steady state (V^{ss}) (305 litre; range 256–363 litre; 4.13–6.05 litre kg^{-1}).

Total body clearance was rapid (1.91 litre min^{-1}) with individual values in the range 1.38–1.96 litre min^{-1}; 23.8–49.3 ml min^{-1} kg^{-1}, estimates of clearance for two individuals exceeding the generally accepted value (1.5 litre min^{-1}) for liver blood flow.

Mean blood concentrations of propofol for the fentanyl and halothane groups were greater than those for the control group at all time points throughout the period. The differences were, however, statistically significant ($P < 0.05$) only at six out of eight sampling times up to 45 min and at 360 min for the fentanyl group, and only at the 30 and 45 min sampling times; that is, shortly after the return of consciousness in the halothane group. There was, however, no apparent temporal trend in the ratios of propofol blood concentration for either treatment group when compared with the control group. Mean blood concentration ratios over the 8-h sampling period were 1.50 ± 0.07 and 1.28 ± 0.06 for the fentanyl and halothane groups, respectively, when compared with the control group.

A pharmacokinetic model-independent method of assessment of the statistical significance of the differences in propofol concentration between treatment groups over the whole sampling period has also been used. Hence, the mean value of the trapezoidal area under the curve to 8 h (AUC_{trap}) for the fentanyl group (93.8 μg min ml^{-1}) was significantly greater ($P < 0.05$) than the corresponding value for the control group (63.0 μg min ml^{-1}). The AUC_{trap} value for the halothane group (81.8 μg min ml^{-1}) was not significantly different from the values for the two other treatment groups.

Propofol was apparently cleared more slowly by patients pretreated with fentanyl than those in the control group (table II). Individual values of total body clearance for the fentanyl group were within the range 1.08–1.38 litre min^{-1} (19.3–26.2 ml min^{-1} kg^{-1}); the range of individual values for the halothane group patients (1.03–2.26 litre min^{-1}; 22.4–37.7 ml min^{-1} kg^{-1}) was similar to that for the control group.

The volumes of distribution for propofol were appreciably smaller in the fentanyl and halothane groups than in the control group (table II). Individual values of V^{γ} for the fentanyl group (271–596 litre; 5.11–9.31 litre kg^{-1}) and the halothane group (317–577 litre; 6.10–9.62 litre kg^{-1}) were all lower than any in the control group. Similarly, ranges of V^{ss} for the fentanyl group (104–261 litre; 1.86–4.16 litre kg^{-1}) and the halothane group (122–311 litre; 2.65–5.18 litre kg^{-1}) were generally lower than those in the control group.

There was no statistically significant difference between treatment groups for the mean values of the first- or second-phase half-lives. It was not possible to perform a similar comparison for the third-phase half-lives because of our inability to characterize with confidence the third exponential phase in five individuals. However, the ranges of individual values for the fentanyl group (148–318 min) and the halothane group (144–213 min) were similar to that obtained for the control group.

DISCUSSION

Apnoea occurred quite frequently with the Cremophor formulation of propofol (Briggs et al., 1981) and, as one would expect, fentanyl given i.v. appeared to increase the apnoeic effect. The greater incidence of apnoea in patients pretreated with fentanyl may also be related to the greater blood concentrations of propofol observed in this group.

Recovery from anaesthesia with propofol was satisfactory when using either fentanyl or nitrous oxide to give the necessary additional analgesia (Briggs, Dundee et al., 1982). The mean recovery time after maintenance with halothane was 2–3 times longer than those for the other two groups; this probably reflects the relatively slow clearance of halothane.

The pharmacokinetics of propofol for control patients could be described by a three-compartment open mammalian model. During its mixing time (up to 2 min) within the blood volume, propofol distributed appreciably from blood and by this time equilibria had been established between blood and one or more highly perfused organs. Further distribution over the period up to 15 min after administration was very rapid with a half-life of about 3 min.

The very high values for both V^{ss} and V^{γ} (5 litre kg^{-1} and 13 litre kg^{-1}, respectively) indicate that propofol is extensively distributed from blood. Individual values of V^{γ} were, however, two to three times the corresponding values of V^{ss}. This high ratio suggests that, whereas the majority of the dose is eliminated rapidly, a small proportion is eliminated slowly. Individual values for k_{31} ($3–6 \times 10^{-3}$ min^{-1}), the rate constant for transfer from the third compartment to the central compartment, were only a small proportion of values for k_{10} ($4–16 \times 10^{-2}$ min^{-1}), the rate constant of elimination from the central compartment. This confirms that the slow rate of propofol transfer from the third compartment, probably comprising fat, into the central compartment, constrains the metabolic clearance rate of propofol during the final exponential phase. On this basis, clearance of propofol during the middle exponential phase probably reflects the unconstrained metabolic clearance of propofol from blood.

As propofol is metabolized before excretion (Simons et al., 1985), the liver is probably the main eliminating organ. Clearance values for all control group patients were high and it is likely, therefore, that the clearance of propofol is limited by the total blood supply to the liver; however, contributions from extrahepatic metabolic processes cannot be excluded.

Throughout the sampling period the mean propofol blood concentrations in patients pretreated with fentanyl were on average 50% higher than those for patients maintained with nitrous oxide only. This resulted in a comparatively lower estimate of total body clearance for the fentanyl group. The difference was significant when AUC_{trap} values were compared and may result from either competitive metabolism between propofol and fentanyl or a reduction in the total blood supply to the liver in the fentanyl group. Hughes, Campbell and Fitch (1980) and Thompson and colleagues (1986) have previously observed decreases in liver blood flow in animals anaesthetized with volatile and i.v. anaesthetics, respectively. Despite the lower clearance in the fentanyl group, half-lives for the three exponential phases were no longer than those in the control patients. This appears to be a reflection of the apparently lower volume of distribution of propofol in the fentanyl group. Although it was not possible to test the statistical significance of the observed differences in V^{ss} and V^{γ}, individual values (when standardized for body weight) were generally lower in the fentanyl group when compared with the control group. Similar, but much greater, reductions in the clearance and volume of distribution of etomidate given as a bolus dose during steady state (10-μg litre^{-1}) plasma concentrations of fentanyl have been reported by Schüttler and colleagues (1982).

The mean propofol concentrations for the halothane group were intermediate between those of the other two treatment groups. Clearance estimates for the halothane and control groups were similar; as a result, the small differences in blood concentrations observed between these groups are unlikely to be of any clinical significance.

The clinical significance of the observed differences in the pharmacokinetics of propofol when used in conjunction with fentanyl will depend on the treatment regimen used. When propofol is used merely as an induction agent, with maintenance of anaesthesia by inhalation anaesthetics, the higher propofol concentrations in the fentanyl group compared with those in the control group are unlikely to make any clinically significant difference to the observed recovery time for procedures lasting up to 15 min; this is attributable to the very rapid distribution of propofol from the blood during this period. For procedures lasting longer than 15 min, propofol concentrations at the end of the procedure will almost certainly be less than those necessary to maintain anaesthesia (1 μg ml^{-1}) and under these circumstances the recovery time would be controlled by the clearance of the inhalation agent from blood.

However, in procedures where propofol is used to maintain anaesthesia by either repeat bolus doses or continuous infusion, the higher propofol blood concentrations and lower propofol clearance in patients pretreated with fentanyl would be expected to be clinically significant. Hence, it would be predicted that, irrespective of any direct contribution from fentanyl to the level of hypnosis, the dose of propofol necessary to achieve a given depth of anaesthesia would be smaller in patients pretreated with fentanyl. This prediction is consistent with the findings of Prys-Roberts (personal communication) when administering a zero-order infusion of the Cremophor formulation of propofol in the presence and absence of fentanyl.

The secondary peaks observed in the propofol blood concentration profiles soon after the return of consciousness are probably linked with a change in the distribution of propofol during recovery. This effect may be local to the sampling site, being caused by the rapid establishment of a new equilibrium between propofol in the sampling limb tissue and blood. Alternatively, the observation may reflect a systemic change in the volume of distribution of propofol. Elfstrom (1979) has discussed changes in regional blood flow and cardiac output which occur during recovery from anaesthesia; changes of this nature may be responsible for the apparent changes in the distribution of propofol.

Similar secondary peaks were observed in thiopentone concentration profiles by Morgan and co-workers (1981) around the time of delivery in patients undergoing Caesarean section; they postulated that these peaks could be caused by disruption to normal blood flow at parturition. Moore and McBride (1978) observed secondary peaks in the diazepam plasma profiles up to 18 h after dosing and during labour; they concluded that these discontinuities resulted from physiological changes related to posture and exercise as the patients first became ambulant after delivery.

The co-administration of inhalation anaesthetics in these patients has precluded a direct correlation between waking and propofol blood concentration. However, the mean blood concentration of propofol of approximately 1 μg ml^{-1} at the mean waking time for each treatment group was similar to the value reported by Adam and colleagues (1983) at "eyes open on command" (1.05 μg ml^{-1}) in patients who received an induction dose (2.0 mg kg^{-1}) of the Cremophor formulation of propofol.

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RECOVERY FROM OUTPATIENT ANAESTHESIA: A COMPARISON OF INCREMENTAL PROPOFOL AND PROPOFOL–ISOFLURANE

K. R. MILLIGAN, D. P. O'TOOLE, J. P. HOWE, J. C. COOPER AND J. W. DUNDEE

SUMMARY

Propofol was used to induce anaesthesia in 60 patients undergoing minor outpatient gynaecological procedures. Maintenance was with 66% nitrous oxide in oxygen, plus either isoflurane or 10-mg increments of propofol. Recovery was assessed using both clinical and psychomotor criteria and the results compared with those obtained in a non-anaesthetized control group. As far as the two test groups were concerned, initial recovery was more rapid in the incremental propofol group but, by 1 h after surgery, there were no differences between all three groups.

For social and economic reasons, outpatient surgery continues to increase in popularity. The anaesthetist is required to provide a smooth induction and good operating conditions, and to ensure rapid recovery with minimal postoperative sequelae. The hindered phenol, propofol, has proved to be a suitable induction agent for outpatient anaesthesia (McKenzie and Grant, 1985; O'Toole et al., 1987).

Although it has been shown that propofol, used as the main anaesthetic agent, provides satisfactory anaesthesia for minor gynaecological procedures (Redfern, Stafford and Hull, 1985), recovery from this type of anaesthesia has not been investigated in detail. The present study investigated the recovery characteristics of two anaesthetic techniques in which propofol plus nitrous oxide was used, *viz.*:

(a) propofol induction with propofol maintenance or

(b) propofol induction with isoflurane maintenance.

Recovery from anaesthesia was assessed using a combination of clinical and psychomotor methods.

PATIENTS AND METHODS

Sixty healthy, unpremedicated women aged 16–55 yr, weighing 45–80 kg and due to undergo uterine dilatation and currettage were studied. Patients taking psychoactive medication or having a history of allergy were excluded. The design of the study was approved by the local Medical Ethical Research Committee and informed consent was given by all patients.

Anaesthesia was induced with propofol (Diprivan) 2.5 mg kg^{-1} injected over 20 s to a large forearm vein, and continued with 66% nitrous oxide in oxygen through a Magill (Mapleson A) breathing system.

Patients were randomly allocated to two equal groups, to receive either incremental propofol (P) or isoflurane (F) as the principal maintenance agent. Group P received 10-mg increments of propofol as required to permit surgery to proceed. Group F patients breathed up to 3% isoflurane initially, reducing to 1% once the cervix had been dilated. Signs of inadequate anaesthesia were taken as resistance to elevating the legs to the lithotomy position, spontaneous movement, in-

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TABLE I. *Patient age, weight and duration of anaesthesia with the cardiorespiratory changes at induction (mean ± SEM). * P < 0.05 compared with group P*

	Group P	Group F	Group C
Age (yr)	29.2±1.3	31.3±1.7	29.5±1.4
Weight (kg)	59.6±1.7	57.3±1.7	61.2±1.9
Increase in heart rate (%)	8.9±2.5	11.2±1.4	
Decrease in systolic AP (%)	7.5±1.5	10.8±1.4	
No. of patients with apnoea > 60 s	6	4	
Duration (min)	9.7±0.6	12.9±1.7*	

TABLE II. *Initial clinical recovery times (mean ± SEM)*

Time (min) to	Group P	Group F
Eye opening	3.83±0.43	7.32±0.51
Giving DOB	4.52±0.48	7.70±0.51
Orientation	4.57±0.46	7.75±0.50

TABLE III. *Choice reaction times (ms) (mean ± SEM) before and after operation. * P < 0.05 compared with control; † P < 0.05 compared with control and incremental propofol*

	Unanaesthetized control	Incremental propofol	Propofol + isoflurane
Before operation	553±23	554±20	559±24
After operation			
20 min	501±19	545±15*	585±23*
40 min	458±16	466±11	511±19†
60 min	440±15	447±9	478±17

creasing heart rate or arterial pressure, breath holding or increasing rate or depth of ventilation. The duration of apnoea associated with induction was noted and heart rate and arterial pressure measured at 2-min intervals.

The duration of the procedure was recorded as the time from the start of induction until the completion of the surgery.

Recovery was assessed by a second anaesthetist unaware of the anaesthetic technique used. Initial clinical recovery was taken as the time from the end of surgery until the patient could:

(a) open her eyes on command,
(b) give her correct date of birth (DOB) and
(c) demonstrate orientation in time and place.

Subsequent clinical recovery, that is, the patient's alertness and co-ordination, was subjectively assessed at 20, 40 and 60 min after surgery. Alertness was scored using a 4-point scale (4 = fully awake; 3 = drowsy but awake; 2 = sleeping but rousable; 1 = unrousable) and co-ordination by straight-line walking and Romberg's test.

Psychomotor testing consisted of "four choice reaction times"(CRT) (Wilkinson and Houghton, 1975) and "*p* deletions" (Dixon and Thornton, 1973). For CRT testing the patient scanned an array of four coloured bulbs which lit on a random basis. As soon as a light appeared the patient pressed a corresponding button to extinguish it. The response time was recorded on magnetic tape and subsequently decoded and analysed using an Apple IIe computer. For *p*-deletions patients were presented with a page containing lines of random letters. They searched through these, deleting any *p* encountered; the score was taken as the number of lines completed minus the number of *p* missed. The times allowed for CRT testing and *p* deletions were 150 s and 180 s, respectively. To familiarize the patient with the apparatus, the testing was carried out twice in the preoperative period, the results of the first series being discarded and the results of the second series being taken as preoperative baseline values. Subsequent testing was carried out at 20, 40 and 60 min after the operation. Any patient showing an improvement of more than 100% on baseline CRT values was replaced in the study, since it was considered that they demonstrated initial inadequate familiarity with the reaction timer. One group F patient was replaced.

A control group (C) consisting of 30 gynaecological patients awaiting operation were included for purposes of comparison and underwent psychomotor testing identical to that of the other two groups.

The results were analysed statistically using the Mann–Whitney *U* test, independent *t* test, analysis of variance, χ^2 and Fisher's exact probability test where appropriate. Findings are expressed as mean ± SEM.

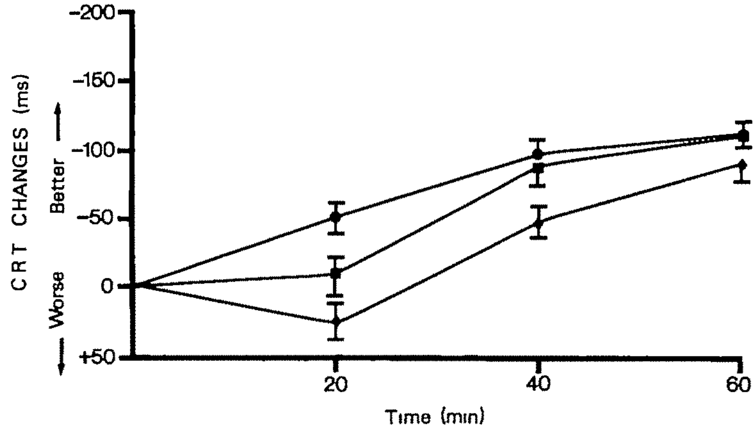

FIG. 1. Changes in CRT (ms) (mean ± SEM) from preoperative baseline values. ● = Controls; ■ = propofol; ◆ = propofol–isoflurane.

TABLE IV. *Preoperative* p *deletion scores and subsequent post-operative changes (mean ± SEM).* * P < *0.05, compared with C*

	Group C	Group P	Group F
Before operation	16.4 ± 1.8	15.8 ± 0.9	14.3 ± 1.9
After operation			
20 min	+2.57 ± 1.6	+0.37 ± 1.5	−1.60 ± 1.4*
40 min	+5.77 ± 1.2	+5.90 ± 1.1	+5.47 ± 1.7
60 min	+5.87 ± 1.6	+7.07 ± 0.9	+7.97 ± 1.6

RESULTS

The groups were broadly comparable with respect to age and weight. The duration of anaesthesia for group P was significantly ($P < 0.05$) shorter, reflecting the more rapid onset of adequate anaesthesia with a total i.v. technique (table I).

There were no significant differences as regards cardiorespiratory effects in the two test groups, and intraoperative apnoea did not occur with the incremental administration of propofol.

Group P received an average of 7.53 ± 0.71 increments, the mean maintenance dose being 51 % of the induction dose. This gave an average administration rate of 0.137 ± 0.011 mg kg^{-1} min^{-1}.

Initial clinical recovery was significantly ($P < 0.01$) faster in the incremental propofol (P) group using all three end points (table II).

There were no statistical differences between the groups with respect to subsequent clinical recovery. Fifteen patients in group P were still ataxic 20 min after operation, compared with 18 in group F, but only one patient in each was still affected by 40 min and none by 60 min. The majority of patients in both groups were fully awake (alertness score 4) by 20 min after the operation (25 in P and 24 in F). One in each group was still drowsy at 40 min after operation, but none at 60 min.

Table III summarizes the choice reaction times. At 20 min there were no statistical differences between the anaesthetized groups and both were significantly slower than the unanaesthetized group C ($P < 0.05$). By 40 min group P had achieved the same CRT values as group C and both these groups were significantly better than group F ($P < 0.05$). By 60 min into the post-operative period there were no statistical differences among the groups, although group F still demonstrated the least improvement. The changes from baseline CRT values are illustrated in figure 1.

The *p* deletion scores are shown in table IV. The patients who received isoflurane showed a statistically significant deterioration at 20 min, in contrast to the improvement seen in the other two groups. There were no statistical differences between the groups at any other time.

Minor postoperative sequelae were uncommon in both groups, headache occurring in one patient in group P and two in group F. Nausea occurred twice in group P and three times in group F, but no patient vomited. An interesting feature of the recovery was a tendency to euphoria in some patients who received propofol for maintenance. No patient expressed dissatisfaction with her anaesthetic.

DISCUSSION

Adequate recovery from outpatient anaesthesia requires a rapid return to street fitness and both propofol and isoflurane would appear to offer advantages in this area. Isoflurane has a low blood solubility with rapid elimination, and has been shown to provide satisfactory recovery from outpatient anaesthesia (Kortilla and Valanne, 1985).

The pharmacological profile of propofol (rapid redistribution, non-cumulation) (Cockshott, 1985) suggests that it also possesses some of the desirable features of an agent suitable for use in outpatients. The present study, and those of other investigators (McKenzie and Grant, 1985; Redfern, Stafford and Hull, 1985) confirm this view. Induction with propofol was smooth and rapid, pain on injection was minimized by administration via a large forearm vein, and the induced cardiorespiratory depression caused no clinical problems.

The present study shows that a total i.v. technique, using propofol as the principal anaesthetic agent, produces recovery superior to a propofol–isoflurane sequence. The technique is eminently suitable for procedures of short duration, providing both a quick onset of adequate anaesthesia and a rapid "clear-headed" recovery. Changes in heart rate and arterial pressure are a poor guide to the depth of propofol anaesthesia, a finding confirmed by others (Robinson, 1985; Walmsley, McCleod and Ponte, 1986). Alterations in the ventilatory pattern proved more useful, and increments of anaesthetic were administered in response to increasing rate and depth of ventilation. This allowed anticipation of lightening anaesthesia and avoided the problem of having to administer large doses of propofol to control patient movement. By more accurately titrating the dose to the patient's requirements, the total amount of propofol required was reduced.

Postoperative sequelae were uncommon in both groups and patient acceptability was high.

In conclusion, recovery was rapid when propofol was used as the principal anaesthetic agent for short procedures.

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PROPOFOL–FENTANYL ANAESTHESIA FOR CORONARY BYPASS SURGERY IN PATIENTS WITH GOOD LEFT VENTRICULAR FUNCTION

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SUMMARY

The haemodynamic effects of propofol–fentanyl anaesthesia for elective coronary bypass surgery were studied in 15 patients with good left ventricular function. The induction dose of propofol was 1.5 mg kg^{-1}. The mean infusion rate during maintenance was 5.15 mg kg^{-1} h^{-1} (range 4.05–8.82 mg kg^{-1} h^{-1}). The total dose of fentanyl given in the pre-bypass period was 32 µg kg^{-1}. Induction of anaesthesia was associated with significant ($P < 0.05$) decreases in systolic (−28%) and diastolic (−23%) pressures, systemic vascular resistance (−25%) and left ventricular stroke work index (LVSWI) (−32%). The decrease in LVSWI ($P < 0.05$) during induction and maintenance with unchanged filling pressures, indicated myocardial depression. Clinical signs that could reflect myocardial ischaemia were not observed during the operation. There were no changes in the concentrations of the cardiac enzymes in the postoperative period and ECG morphology was unchanged.

Although the efficacy of propofol—as an induction agent—has been studied in patients with coronary artery disease (Patrick et al., 1985), the haemodynamic effects of a maintenance technique, in which propofol was infused continuously in patients about to undergo elective coronary bypass surgery, have not been reported. This study describes the haemodynamic effects associated with induction of anaesthesia using propofol, and the continuous infusion of propofol (supplemented with fentanyl) during the pre-bypass period.

PATIENTS AND METHODS

The design of the study was approved by the Ethical Committee of the Antwerp University Hospital.

Fifteen patients with good left ventricular function (ejection fraction > 55% and left ventricular end diastolic pressure < 14 mm Hg), scheduled for elective coronary bypass surgery were included in the study. Mean age was 53 ± 9 (SD) yr, average weight 75.6 ± 11.2 kg and mean body surface area was 1.87 ± 0.17 m^2. All patients had angiographically proven coronary artery disease (two- or three-vessel disease); no patient had significant left main coronary artery stenosis. Thirteen patients were taking beta-adrenoreceptor antagonists. Five patients had a history of previous infarction, and four other patients had unstable angina. Individual data are presented in table I.

Premedication consisted of fentanyl 0.002 mg kg^{-1} plus droperidol 0.01 mg kg^{-1} and glycopyrrolate 0.03 mg kg^{-1} given i.m. 1 h before surgery, as well as the normal oral medication appropriate to each patient.

Upon arrival of the patient in the operation theatre the electrocardiogram (leads 1, 11 and V5) was continuously displayed. Two large-bore venous cannulae and a 20-gauge Teflon radial arterial catheter were placed under local anaes-

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TABLE I. *Clinical data of the investigated patients. All patients received coronary vasodilator therapy. BSA = body square area; NYHA = New York Heart Association classification; AMI = acute myocardial infarction*

No.	Sex	Age (yr)	Weight (kg)	BSA (m^2)	NYHA class	History of AMI	Hyper-tension	Beta-blocking drug	CA^{2+} antagonist
1	F	61	76	1.77	III	+	–	metoprolol	—
2	M	51	60	1.62	IV	–	–	metoprolol	nifedipine
3	M	50	84	2.00	III	+	–	metoprolol	nifedipine
4	M	59	64	1.80	II	–	–	propranolol	—
5	M	51	75	1.90	IV	–	–	metoprolol	diltiazem
6	M	50	78	1.90	II	–	–	metoprolol	nifedipine
7	M	69	68	1.75	IV	–	–	—	verapamil
8	M	42	75	1.93	IV	–	–	atenolol	—
9	M	61	90	2.11	III	+	+	—	nifedipine
10	M	43	60	1.64	III	+	–	atenolol	—
11	M	58	80	1.92	II	–	+	metoprolol	nifedipine
12	M	67	87	2.09	II	–	–	metoprolol	nifedipine
13	M	40	84	2.01	III	–	–	atenolol	—
14	F	65	58	1.53	III	–	–	metoprolol	nifedipine
15	M	42	95	2.09	III	+	–	metoprolol	nifedipine

thesia. A flow-directed balloon-tipped thermodilution catheter (7F triple lumen catheter, Edwards Laboratories) was introduced to the pulmonary artery via the right internal jugular vein using a 7F Cordis introducer. Placement of invasive monitoring catheters in awake, premedicated patients has been shown not to alter cardiovascular variables (Waller, Zaiden and Kaplan, 1982). Pressure systems were assessed for adequacy of their dynamic responses (Gardner, 1981).

The following haemodynamic data were obtained before the induction of anaesthesia: heart rate; systolic and diastolic arterial pressures; systolic and diastolic pulmonary artery pressures; pulmonary capillary wedge pressure and central venous pressure. Cardiac output was measured (in triplicate) by the thermodilution method using 5% dextrose 10 ml in water at 0 °C injected during the expiratory phase. From these data, cardiac index, systemic vascular resistance and left ventricular stroke work index were calculated.

Anaesthesia was induced with diazepam 0.1 mg kg^{-1}, fentanyl 0.008 mg kg^{-1} and propofol 1.5 mg kg^{-1} given consecutively over 30 s. Pancuronium 0.1 mg kg^{-1} was administered and the lungs ventilated manually with oxygen (via an anaesthetic face mask) until intubation. After intubation of the trachea, ventilation was controlled mechanically with a 900 C Siemens Servo ventilator (60% oxygen in air, rate 14 b.p.m, and tidal volume according to the arterial $P\text{CO}_2$, which was kept between 4.7 and 5.3 kPa).

The induction dose of propofol was followed by a continuous infusion of propofol. The infusion rate was adjusted in response to changes in systemic arterial pressure, with a maximum rate of 9 mg kg^{-1} h^{-1}. Before sternotomy an additional dose of fentanyl 0.025 mg kg^{-1} was given.

Haemodynamic data were recorded and calculated at the following time intervals: before induction, 3 min after induction, 3 min after intubation, before and 3 min after sternotomy and before aortic cannulation. The study was discontinued at the start of extracorporeal circulation.

The following indices of myocardial ischaemia were evaluated every 5 min during the procedure: ST-depression (> 1 mm) in V5, increase in pulmonary capillary wedge pressure (PCWP) or appearance of prominent PCWP v-waves.

Before cardiopulmonary bypass (CPB) was started, heparin 300 u kg^{-1} was given i.v.; a subsequent dose of pancuronium 0.1 mg kg^{-1} was given.

Pump priming consisted of 2000 ml of an isotonic solution and 500 ml of a 20% human albumin solution. CPB was conducted using a Bentley TM-10 disposable bubble oxygenator and Stockert/Cobe roller pumps. During CPB the lungs were not ventilated but were allowed to collapse partially with a static inflation pressure of 3 mm Hg.

Patients were cooled during CPB to a rectal temperature of 25 °C. Non-pulsatile flow was used at 2.4 litre m^{-2} min^{-1} with a mean perfusion

TABLE II. *Propofol–fentanyl anaesthesia for coronary bypass surgery: haemodynamic data (mean ± SD). * Significantly different from T1 ($P < 0.05$). HR = Heart rate; APsyst = systolic arterial pressure; APdiast = diastolic arterial pressure; SVR = systemic vascular resistance; Ppsyst = systolic pulmonary artery pressure; Ppdiast = diastolic pulmonary artery pressure; PCWP = pulmonary capillary wedge pressure; CVP = central venous pressure; CI = cardiac index; LVSWI = left ventricular stroke work index. T1 = before induction, T2 = 3 min after induction; T3 = 3 min after intubation; T4 = before sternotomy; T5 = 3 min after sternotomy; T6 = before aortic cannulation*

	T1	T2	T3	T4	T5	T6
HR (beat min^{-1})	62±12	62±10	64±10	57±8	59±8	65±14
APsyst (mm Hg)	142±24	102±10*	106±14*	115±16*	114±12*	101±17*
APdiast (mm Hg)	64±10	49±5*	50±7*	60±10	62±11	55±11*
SVR (dyn s cm^{-5})	1037±221	773±112*	802±150*	1138±304*	1225±370*	1042±393
*P*psyst (mm Hg)	28±8	25±6	26±7	25±6	24±8	20±5*
*P*pdiast (mm Hg)	13±5	11±4	10±4*	10±3*	10±5*	8±3*
PCWP (mm Hg)	13±4	13±4	12±4	13±4	12±4	10±4
CVP (mm Hg)	6±3	6±4	5±4	6±3	6±3	5±3
CI (litre min^{-1})	3.6±0.7	3.4±0.5	3.4±0.6	2.9±0.6*	2.8±0.7*	2.9±0.7*
LVSWI (g m m^{-2})	62±17	42±10*	42±10*	46±11*	45±13*	38±12*

pressure of 50 mm Hg. In order to keep mean perfusion pressure constant, either phenylephrine or an infusion of propofol was used to control systemic vascular resistance, when necessary. St Thomas' Hospital cardioplegic solution (1000 ml at 4 °C) and topical cooling of the myocardium were used for myocardial protection.

The infusion of propofol was discontinued at the end of CPB. Fentanyl 0.010 mg kg^{-1}, was given after weaning from CPB.

Results were analysed for statistical significance using analysis of variance. The null hypothesis was rejected if $P < 0.05$. Where appropriate, analysis of variance was followed by the Walker Duncan Adaptive Procedure. Significance was accepted when $P < 0.05$.

RESULTS

The results are summarized in table II.

Induction

Induction of anaesthesia was associated with significant ($P < 0.05$) decreases in systolic (−28%) and diastolic (−23%) pressures, systemic vascular resistance (−25%) and left ventricular stroke work index (−32%). The decrease in systemic vascular resistance was not associated with an increase in cardiac index or heart rate. Left and right filling pressures were not affected by induction with propofol.

Maintenance

The mean infusion rate was 5.15 mg kg^{-1} h^{-1} (range 4.05–8.82 mg kg^{-1} h^{-1}). When haemodynamic data before, and 3 min after, intubation were compared, no significant differences were found for the observed and calculated variables, except for an increase in systemic vascular resistance ($P < 0.05$). During intubation, however, systolic and diastolic arterial pressures increased in eight of the 15 patients (+26% and +28%, respectively). However, in all these patients the peak systolic arterial pressure at intubation was still less than the awake value. The increase in arterial pressure was transient; vasodilator therapy was not required and the change in pressure was not acompanied by an increase in heart rate.

When haemodynamic data before, and 3 min after, sternotomy were compared, no significant difference could be observed, except for an increase in systemic vascular resistance. In 12 of the 15 patients (80%) arterial pressure remained constant during sternotomy and sternal spread. In two patients there were moderate, but transient, increases in systolic and diastolic arterial pressures, with peak systolic pressure lower than the awake value. In one patient, sternotomy and sternal spread were associated with a hypertensive reaction (peak systolic pressure 188 mm Hg), but this was easily corrected with nitroglycerin (infused at a rate of 1.5 $\mu g\ kg^{-1}\ min^{-1}$).

The significant decrease in left ventricular stroke work index after induction remained significant during maintenance ($P < 0.05$). Left and right filling pressures were constant during maintenance.

Systemic vascular resistance increased continuously during maintenance; this effect was most pronounced in the period after intubation but before sternotomy. The increase in systemic vascular resistance was associated with a decrease in cardiac index ($P < 0.05$).

During the maintenance of anaesthesia, systolic arterial pressure remained less than the awake value ($P < 0.05$).

Bypass and post-bypass period

Mean duration of CPB was 107 min ±32 (SD). Mean aortic cross clamping time was 65 min ±22. Saphenous aorta–coronary bypass graftings ranged from one to five (mean three) distal anastomoses. In addition, in 13 of the 15 patients the left internal mammary artery was used for an end-to-side anastomosis with the LAD (left anterior descending coronary artery). In three of these patients a proximal stenosis in a diagonal branch of the LAD was bypassed with a side-to-side anastomosis between the left internal mammary artery and the diagonal branch.

Mean propofol infusion rate during CPB was 2.57 $mg\ kg^{-1}\ h^{-1}$ (range 0–8.41 $mg\ kg\ h^{-1}$). Increments of phenylephrine 1 mg were given in 11 patients, with a maximum dose of 5 mg, especially during the first minutes of CPB, in order to maintain the perfusion pressure at 50 mm Hg.

Weaning from CPB, after rewarming to a rectal temperature of 35 °C, was straightforward in 14 patients. All these patients had a normal (sinus) cardiac rhythm at the end of CPB; they came of bypass with normal left and right filling pressures, without inotropic support, except for calcium chloride 1 g. One patient with a third-degree AV block needed ventricular pacing as well as a high preload before coming off CPB.

Fifteen minutes after the patients were weaned from CPB, systolic and diastolic arterial pressures were 106 mm Hg ±14 (SD) and 58 mm Hg ±8. Mean heart rate was 83 beat min^{-1} ±9. Mean cardiac index was 3.5 litre $min^{-1}\ m^{-2}$ ±0.8 and calculated mean systemic vascular resistance was 810 dyn s cm^{-5} ±195. Mean pulmonary capillary wedge pressure was 15 mm Hg ±4.

ST-depression, increases in pulmonary capillary wedge pressure or prominent PCWP v-wave, were not observed during anaesthesia and surgery. After surgery, the concentrations of cardiac enzymes (CK, CK-MB, LDH, ASAT, ALAT) were within normal limits in all patients. Postoperative ECG morphology was identical to preoperative ECG morphology in all patients.

DISCUSSION

Maintenance of an adequate myocardial oxygen balance is essential during coronary artery bypass surgery. An increase in cardiac work implies a risk that myocardial oxygen demand could exceed supply, distal to the coronary stenosis. This may result in ischaemia or even infarction. An imbalance between supply and demand may be prevented by an anaesthetic technique which causes myocardial depression or assures complete absence of any hypertensive response to noxious stimuli such as intubation and sternotomy. High-dose fentanyl anaesthesia is usually chosen for its minimal effects on cardiovascular dynamics, but the frequency of break-through hypertension is, in our opinion, unacceptably high (de Lange et al., 1982; Sebel et al., 1982; Wynands et al., 1983). Until now, intentional myocardial depression has involved the use of volatile anaesthetics (Moffitt and Sethna, 1986).

It can be concluded from the decrease in left ventricular stroke work index, with no change in atrial filling pressures, that propofol–fentanyl anaesthesia has myocardial depressive properties. Furthermore, the fact that the significant decrease in systemic vascular resistance after induction and intubation was not associated with an increase in cardiac index supports the thesis of a depressed myocardial pump function.

The reduction in arterial systolic and diastolic pressures observed on induction is comparable to the results of other authors who studied propofol as an induction agent in patients with coronary artery disease (Al-Khudhairi et al., 1982; Patrick et al., 1985). In the study by Patrick and colleagues (1985), systolic arterial pressure decreased below 100 mm Hg in eight of the 10 patients after induction with propofol 1.5 mg kg^{-1}. In two patients it decreased to less than 70 mm Hg. In our group only five of 15 patients had a systolic arterial pressure less than 100 mm Hg after induction, the lowest arterial pressure observed being 88 mm Hg. This difference was probably the result of the greater left and right filling pressures before induction in our group. Mean pulmonary capillary wedge pressure in our patients was 13 mm Hg, whereas it was 6.6 mm Hg in the patients studied by Patrick and colleagues (1985).

The significant decrease in diastolic arterial pressure on induction and during intubation must result in a decrease in coronary perfusion. This is counterbalanced by a reduction in oxygen demand: systolic arterial pressure is decreased, when compared with the awake value, and myocardial function is depressed in the presence of a reduced afterload. Therefore, it may be concluded that during induction and intubation the heart is not more at risk of ischaemia than before induction. This is supported by the absence of ST-depression, or increased pulmonary capillary wedge pressure.

One patient became hypertensive during sternotomy and sternal spread, and required an infusion of nitroglycerin to control the arterial pressure. A higher incidence has often been recorded during high-dose fentanyl anaesthesia in patients with good left ventricular function, taking beta-adrenoreceptor antagonists. Moffitt and coworkers (1984) reported that two out of 10 patients needed sodium nitroprusside after sternotomy. Waller and associates (1981) reported that eight out of 12 patients required additional anaesthetic drugs and an infusion of nitroglycerin to control hypertension. Sonntag and colleagues (1982) recorded a systolic arterial pressure of more than 200 mm Hg in four out of nine patients after sternotomy. Edde (1981) studied the haemodynamic changes before, and after, sternotomy in patients anaesthetized with fentanyl 50 µg kg^{-1} given at induction as a single i.v. bolus. All the patients, most of whom were taking beta-adrenoreceptor antagonists, became hypertensive after sternotomy and required vasodilator treatment.

The degree of beta-adrenergic blockade during anaesthesia influences the likelihood of hypertension during intubation, skin incision, sternotomy and sternal spread (de Lange et al., 1982; Moffitt et al., 1984). Our patients received their normal dose of beta-blocking drug up to the day of surgery.

The decreases in diastolic and mean arterial pressures during induction and early maintenance caused a decrease in coronary blood flow. However, myocardial oxygen demand seemed to decrease more than the decrease in oxygen supply, since there was neither ST-depression nor an increase in pulmonary capillary wedge pressure. However, we must consider that, even in the absence of ST-depression, the heart can become ischaemic and produce lactate (Moffitt et al., 1986). The adequacy of myocardial oxygen balance can also be assessed by the endocardial viability ratio (Hoffman and Buckberg, 1978) but this ratio must be used with caution in patients with coronary artery disease. In myocardial regions supplied by a stenotic coronary artery, the critical endocardial viability ratio may increase to an unknown extent. This limitation still exists when more sophisticated techniques are used to assess myocardial metabolism, such as coronary sinus catheterization. Even when supraselective coronary sinus blood sampling is performed, one cannot state with absolute certainty that segmental ischaemia will always be detected (Sethna and Moffitt, 1986).

If periods of regional myocardial ischaemia did occur during induction and maintenance, they were not associated with ST-depression or increases in capillary wedge pressure. Although it may not be stated that the heart was never at risk during the procedure, there was no evidence of myocardial infarction.

Postoperative ECG morphology was unchanged and all the concentrations of the cardiac enzymes were normal.

In conclusion, this study demonstrated that propofol–fentanyl anaesthesia was an adequate technique for coronary bypass surgery in patients with good left ventricular function taking beta-adrenoreceptor antagonists. Myocardial depression was associated with a low incidence of hypertensive reactions to noxious stimuli. Clinical signs of ischaemia were not observed and peroperative infarction did not occur.

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ARTERIAL OXYGENATION AFTER MAJOR HEAD AND NECK SURGERY INVOLVING TRACHEOTOMY†

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SUMMARY

Changes in vital capacity, and in arterial P_{O_2} and P_{CO_2}, were studies after major head and neck surgery involving tracheotomy and after surgery on the upper abdomen. After major head and neck surgery, changes in vital capacity were comparable to those seen after upper abdominal operations, with a decrease on day 1 of 39% recovering to 78% of the preoperative volume by day 7. Arterial P_{O_2} in both groups decreased on day 1 but whereas Pa_{O_2} after upper abdominal surgery was recovering by day 7, Pa_{O_2} in the head and neck group, at day 7, showed no sign of recovery. Arterial P_{O_2} 7 days after major head and neck surgery was 2.3 (±0.4) kPa below the preoperative value ($P < 0.001$).

It is well established that disturbances occur in respiratory function after operation, and that in the postoperative period many patients are hypoxaemic for periods which vary from a few minutes up to several weeks. These disturbances are particularly severe following operations on the body cavities—the thorax or the abdomen (Marshal and Miller, 1965; Bishop and McKeown, 1979). The most severe and most persistent hypoxaemia seen after non-thoracic operations, in the absence of overt chest complications, occurs after upper abdominal surgery. Hypoxaemia is at its worst on the 1st or 2nd day after operation, then starts to recover. Changes in lung volume parallel the changes in blood-gas tensions (Saady, 1974; Craig, 1981). Persistent hypoxaemia is said not to occur after minor surgery or surgery on the extremities (Marshal and Miller, 1965).

There appear to be no data on respiratory function after major head and neck surgery. This could almost be regarded as surgery on an extremity. It involves the soft tissues of the neck and frequently the superficial tissues of the chest wall, but does not normally encroach upon the thoracic nor the abdominal cavities. Surgery for cancer of the head and neck is, however, major surgery involving the upper airway, lasting several hours, entailing significant amounts of tissue damage and frequently leaving the patient with a tracheostomy. This paper describes changes in arterial oxygenation, and in vital capacity, on the 1st and 7th days after operation in patients undergoing major surgery for carcinoma of the head and neck. These changes are contrasted with those occurring over the same period in patients undergoing upper abdominal surgery—vagotomy and pyloroplasty or cholecystectomy.

PATIENTS AND METHODS

Patients

Fourteen patients scheduled to undergo major surgery for carcinoma of the larynx or oropharynx consented to take part in the study. All patients had tracheotomy carried out during the operation and the tracheostomy was still present when the postoperative measurements were made. None had a tracheostomy before operation. In addition, 18 patients were studied who underwent vagotomy and pyloroplasty, or cholecystectomy.

Exclusions. Since the objective of the study was to investigate arterial oxygenation after head and neck surgery in the absence of pulmonary complications, patients who developed overt chest

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complications were withdrawn from the study. Pulmonary complications were defined as the production of purulent sputum accompanied by a temperature in excess of 38 °C persisting for longer than 24 h, or physical or radiological signs of pulmonary collapse or consolidation. Chest x-rays were taken only when there were clinical indications to do so.

Head and neck surgery

Arterial Po_2 and Pa_{CO_2} were measured before, and on the 1st and 7th days after, operation. Blood was taken from a radial artery under local anaesthesia with the patient in bed propped up at an angle of 50–60° breathing room air and encouraged to breathe normally. Vital capacity (VC) was measured with a bell spirometer (Mk II Spirometer, PK Morgan Ltd, Chatham,) which was calibrated with a 1-litre syringe. The patients were familiarized with the apparatus before the operation and then, after several practice measurements, were instructed to breathe slowly in their own time from maximum inspiration to maximum expiration. Before the operation the patient breathed into the spirometer via a mouthpiece with the nose occluded, making sure that the lips were well sealed around the mouthpiece. After surgery the spirometer was attached directly to the patient's cuffed tracheostomy tube, again ensuring that the cuff was inflated and there were no leaks.

Upper abdominal surgery

Vital capacity and blood-gas tensions were measured before and after operation in the patients undergoing upper abdominal surgery. Measurements were made on all patients before, and on the 7th day after, the operation but on only five patients on the 1st day after operation.

Arterial Po_2 and Pa_{CO_2} were measured using the same techniques as for the patients having head and neck surgery. Vital capacity was measured using a Vitalograph wedge spirometer (Vitalograph Ltd, Buckingham) and mouthpiece. The nose was occluded and care taken to ensure that there were no leaks around the mouthpiece. Again, the patients were familiarized with the apparatus before taking the measurement. The Vitalograph was calibrated with the same 1-litre syringe as was used to calibrate the bell spirometer.

Blood-gas analyses were performed using a Radiometer ABL2 blood-gas machine (Radiometer, Copenhagen, Denmark) maintained as recommended by the manufacturer. The coefficient of variation of quality control samples analysed by the blood-gas apparatus daily over 1 week was 2.3 % for Po_2 and 2.5 % for Pco_2.

Both groups received i.m. opioids on demand for postoperative pain relief.

RESULTS

Patients

Two patients from the head and neck group and three from the upper abdominal group were withdrawn because of chest complications as defined above. Results are, therefore, complete for 12 patients undergoing head and neck surgery and 15 patients who had upper abdominal surgery. Details of the patients are shown in table I. Patients having head and neck operations were older than the abdominal group ($P < 0.001$). The head and neck group, with one exception, were all male, whereas the patients having upper abdominal surgery were predominantly female.

Arterial Po_2 and Pa_{CO_2} values are shown in figure 1 and the vital capacity results in figure 2. Preoperative vital capacity in the patients having head and neck surgery was 2.85 (±0.26) litre (mean ± SEM) (BTPS) and in the upper abdominal group was 3.40 (±0.30) litre. This difference was not significant but, for clarity, changes in vital capacity are presented as percentage changes from the preoperative volume.

Head and neck surgery

In the patients who had head and neck operations, Pa_{O_2} decreased significantly on day 1 from a preoperative value of 11.9 (±0.4) kPa to 10.3 (±0.5) kPa ($P < 0.001$). By day 7 this had decreased further to 9.6 (±0.3) kPa. This further decrease was not statistically significant. By day 7, Pa_{O_2} was 2.3 (±0.4) kPa below the preoperative value ($P < 0.001$). Arterial Pco_2 did not alter. Vital capacity decreased to 61 % of the preoperative value on day 1 ($P < 0.001$) and by day 7 had increased to 78 % of the preoperative volume ($P < 0.001$).

TABLE I. *Details of patients studied*

	Head and neck surgery	Upper abdominal surgery
n	12	15
Age (yr) (mean, SD)	59 (10)	45 (13)
Male:female	11:1	4:11

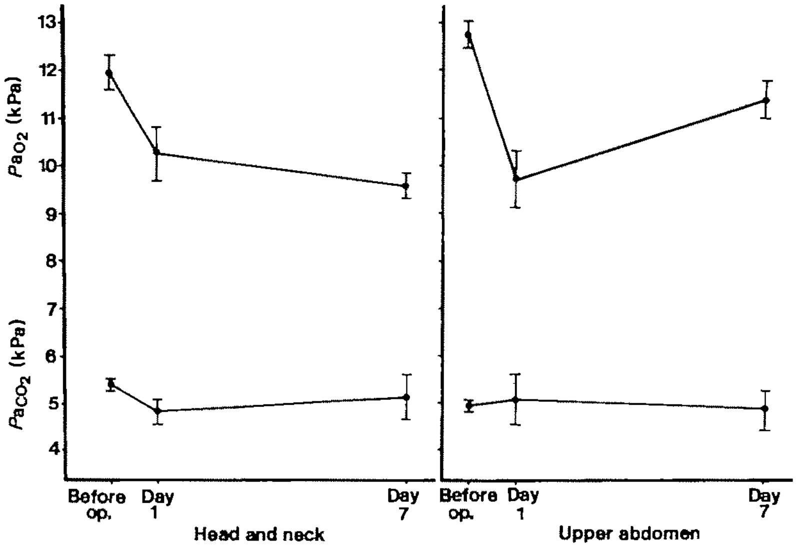

FIG. 1. Mean (±SEM) pre- and postoperative Pa_{O_2} and Pa_{CO_2} in 12 patients undergoing major head and neck surgery and 15 patients having upper abdominal surgery. Values for day 1 for the upper abdominal group are for five patients only.

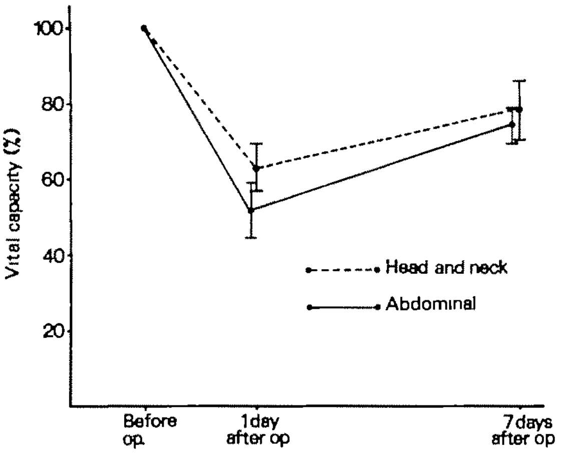

FIG. 2. Changes in vital capacity (mean ± SEM) after major head and neck surgery ($n = 12$) and after upper abdominal surgery ($n = 15$) expressed as a percentage of the preoperative value. Values for day 1 after upper abdominal surgery are for five patients only.

Upper abdominal surgery

Preoperative arterial Po_2 values in the patients undergoing upper abdominal surgery were 12.8 (±0.3) kPa ($n = 15$) and decreased significantly to 9.7 (±0.6) kPa on day 1 ($n = 5$) ($P < 0.001$). Arterial Po_2 increased to 11.4 (±0.4) kPa on day 7 ($n = 15$) ($P < 0.02$). Arterial Pco_2 did not alter. Vital capacity after abdominal surgery decreased on day 1 to 52% of the preoperative volume ($P < 0.001$) (fig. 2). By day 7 it had increased significantly, to 73% of the preoperative value ($P < 0.001$).

DISCUSSION

The two groups of patients described in this study are not directly comparable because of the difference in age and in the sex distribution. In addition, all patients in the head and neck group smoked, whereas only nine of the upper abdominal group did. None of the upper abdominal group were transfused, whereas all the head and neck group received blood, although all blood given to the head and neck patients was subjected to micro filtration before its administration. The decision to use patients having upper abdominal surgery as a "control" group was made in order to provide a comparison with previously published work. Upper abdominal surgery is the type of non-thoracic surgery which produces the greatest decrease in Pa_{O_2} in the period after operation and is the type of surgery in which this hypoxaemia has been most thoroughly investigated. The differences between the two groups (age, sex, etc.) are an inevitable consequence of this choice of control patients, in that they represent differences inherent in the nature of the diseases with which the two groups presented (U.S. Surgeon General,

1982) and in the type of surgery they underwent. The fact that the well-established pattern of a decrease in Pa_{O_2} of around 2.7 kPa on day 1 recovering towards normal values by day 7 has been reproduced in the patients having upper abdominal surgery, demonstrates that the findings in the head and neck group are real and not a result of environmental factors or of methodology.

Results are presented for only five of the abdominal patients on day 1 because the decrease in Pa_{O_2} that occurs on day 1 is so well documented (Palmer and Gardiner, 1964; Diament and Palmer, 1966; Spence and Smith, 1971; Drummond, 1975; Morton et al., 1977; McCollum and Campbell, 1979) that it was considered unethical to subject all the patients to investigation. Results for 15 patients are presented for day 7 because the majority of studies investigating hypoxaemia after upper abdominal surgery have been concerned with hypoxaemia in the immediate postoperative period and present results only up to day 5. Only one study has reported oxygenation at 7 days (McCollum and Campbell, 1979) and few beyond that (Knudsen, 1970; Bishop and McKeown, 1979).

The results show that impairment of arterial oxygenation occurred after major head and neck surgery involving tracheotomy, and that the changes in vital capacity were similar to those after upper abdominal surgery. Arterial P_{O_2} decreased after operation on day 1 but, in contrast to abdominal surgery when Pa_{O_2} was recovering by day 7, the hypoxaemia in the head and neck patients was showing no sign of recovery and appeared in fact to be getting worse. There were no significant changes in Pa_{CO_2} in either group, so none of the changes described can be attributed to alterations in ventilation. Chest x-rays were taken only when there were clinical indications, so it is likely that minor degrees of atelectasis were missed.

It appears to be generally agreed that the cause of most respiratory complications after operation is to be found in the airways (Vickers, 1982). However, quite severe hypoxaemia is seen after upper abdominal surgery in the apparent absence of any overt pulmonary complication. The cause of this hypoxaemia is thought to be an alteration in the relationship between closing volume (CV) and functional residual capacity (FRC) that occurs after operation, so that small airways at the base of the lung start to close at relatively higher lung volumes than before surgery (Spence and Alexander, 1972; Craig, 1981). Certainly, Alexander and colleagues (1973) demonstrated a relationship between increases in alveolar–arterial gradients and a shift in the FRC–CV relationship, but it has never been entirely possible to rule out the effects of small areas of collapse or consolidation that may exist but are undetectable on examination or chest x-ray (Prys Roberts et al., 1967). In the present study, patients who had obvious complications were withdrawn as the object was to look only at the effects of the surgery, not at the incidence or effects of supervening infection or collapse but, as already indicated, areas of pathology which are not detectable clinically may exist in the lung after surgery.

The pattern of change in vital capacity after head and neck surgery was similar to that seen after upper abdominal operations, but the pattern of oxygenation was not. This implies that the aetiology of the hypoxaemia after major head and neck surgery may be different from that seen after operations on the upper abdomen. The differences between the groups referred to earlier—age, smoking habits and blood transfusion—which in the circumstances were unavoidable, must obviously be considered as possible causes of the hypoxaemia seen in the head and neck group. However, previous work has shown that, although arterial P_{O_2} decreases with age (Nunn, 1965) and smokers normally have a lower Pa_{O_2} than non-smokers (Holtz, Bake and Sixt, 1979) neither factor affects the decrease in Pa_{O_2} after operation (Nunn, 1965; Davies and Spence, 1972; Drummond, 1975; Holtz, Bake and Sixt, 1979; McCollum and Campbell, 1979). Micro filtration of micro aggregate debris in transfused blood is another factor that affects arterial oxygenation after massive transfusion (Reul, Beall and Greenberg, 1974), but not after the more moderate transfusion (up to 5 units) (Synder et al., 1979) usually seen with elective surgery. The largest volume of blood given in the present study was 6 units, and all blood transfused was micro filtered.

Another difference between the groups which is not usually taken into account when investigating hypoxaemia is the extent of the surgery. The fact that all the head and neck group were transfused, but none of the upper abdominal group were, implies that the head and neck surgery was the more extensive, with more tissue damage, and accompanied by more of a systemic upset from hypovolaemia etc. There is some indirect evidence that this may affect arterial oxygenation after operation. Morton and Ebert (1974) showed that radiological signs of interstitial pulmonary oedema could be identified after extensive intestinal resection, but not after more limited abdominal surgery such as cholecystectomy. This oedema was accompanied by more severe hypoxaemia. McCollum and Campbell (1979) demonstrated a relationship between severity of hypoxaemia and the postoperative development in femoral vein blood of platelet and fibrin aggregates which, presumably, embolized to the lung. Again, the aggregates were seen in those patients who had the more extensive surgery. Recent work in animals has confirmed this finding and demonstrated an association with a decrease in circulating leucocytes and increases in pulmonary artery pressure (Poskitt et al., 1985). Leucocyte aggregation is involved in development of the adult respiratory distress syndrome (Lloyd, Newman and Brigham, 1984). The work quoted here implies it may be involved in postoperative hypoxaemia.

The other possible cause of the persistent hypoxaemia after surgery on the head and neck could be a combination of the decrease in VC and the presence of a tracheostomy. The change in VC after head and neck surgery was comparable to that after upper abdominal operation, despite the fact that neither the thoracic nor the abdominal cavities were opened. Tracheotomy in dogs has been shown to produce a decrease in FRC (Noguch, Takumi and Achi, 1973) and all the head and neck patients had a tracheotomy at the time the postoperative measurements were made. A decrease in FRC may alter the relationship between closing volume and FRC and produce hypoxaemia by the same sort of mechanism as was proposed for that after upper abdominal surgery (Spence and Alexander, 1972; Craig, 1981). In addition, dry air at room temperature entering the trachea through the tracheostomy could stimulate bronchial secretions and increase bronchomotor tone. This would decrease the diameter of the bronchial lumen and exacerbate the situation further. If this occurs it appears that, in these circumstances, tracheotomy is actually contributing to a disturbance in respiratory function.

Whatever the cause of the persistent low arterial oxygen tensions after head and neck surgery, it is clear that these patients are hypoxaemic after operation, and that the pattern of hypoxaemia is different from that seen after upper abdominal surgery. At 1 week the decrease in Pa_{O_2} was comparable in severity to that seen the 1st day after upper abdominal operations but, unlike abdominal surgery, at 1 week it was showing no sign of recovery. Its aetiology and its duration would be worthy of further investigation.

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VENTILATORY EFFECTS OF MEPTAZINOL AND PETHIDINE IN ANAESTHETIZED PATIENTS

A. LEE AND G. B. DRUMMOND

SUMMARY

The ventilatory effects of three doses of meptazinol (20 mg, 30 mg and 48 mg) were studied in anaesthetized patients and compared with those of pethidine 20 mg. Minute volume, tidal volume, ventilatory frequency, inspiratory and expiratory times were measured and mean inspiratory flow rates calculated. Each patient received a first dose of drug which was followed after 5 min by a second identical dose. After the first injection the ventilatory effects of meptazinol were dose-dependent and meptazinol 20 mg had an effect similar to pethidine 20 mg. Following repeated injection the effects on ventilation were markedly different between the drugs. Carbon dioxide retention and other compensatory mechanisms attenuate the ventilatory depression of meptazinol, but these may be inadequate in the anaesthetized patient.

Meptazinol is a relatively new analgesic agent that has been found to have few ventilatory side effects (Jordan et al., 1979; Cohen et al., 1983). However, it was noted by one of the present authors that the administration of meptazinol i.v. during anaesthesia resulted in profound ventilatory depression. This study was designed to investigate the ventilatory effects of meptazinol in anaesthetized patients.

PATIENTS AND METHODS

Twenty-four fit female patients undergoing minor gynaecological surgery were studied after giving written consent. The study was approved by the local hospital Ethics Committee. The patients were randomly allocated to four groups of six as indicated in table I. No patient was taking medication likely to influence ventilatory control. All patients received temazepam 10 mg orally as premedication 1 h before the commencement of anaesthesia.

Anaesthesia was induced with etomidate 20 mg i.v. and maintained with halothane in oxygen, initially at a 4% inspired concentration, stepping down at 5-min intervals to 3% and then 1.5%. The patients continued to breathe 1.5% halothane in oxygen for 5-min before the start of the study. By this time they were in a stable anaesthetized state as indicated by regular ventilation and stable minute volume. The study was completed before the commencement of surgery. All patients breathed halothane from the same vaporizer (Fluotec Mark 2), the output of which was verified by interferometry before the study. The halothane–oxygen mixture was inspired through a breathing system which led from a standard Boyle anaesthetic machine via a reservoir bag and low resistance spill valve, through a dry gas meter (Parkinson Cowan) and screen pneumotachograph (Mercury Fl) to a close fitting face mask (Portex), incorporating a low resistance, non-rebreathing valve (Ambu Hesse) (fig. 1). The spill valve opened at very low pressures (< 10 Pa at 10 litre min^{-1}), so that gas only passed through the dry gas meter when the patient breathed in. The

TABLE I. *Clinical details of the patients studied (mean values and SD). M20 = Meptazinol 20 mg + 20 mg; M30 = meptazinol 30 mg + 30 mg; M48 = meptazinol 48 mg + 48 mg; P20 = pethidine 20 mg + 20 mg*

Group	Age (yr)	Height (m)	Weight (kg)
P20	37.8 (5.3)	1.62 (0.07)	61 (7.1)
M20	30.7 (8.8)	1.64 (0.10)	60 (16.8)
M30	38.2 (9.6)	1.58 (0.07)	56.7 (8.5)
M48	34.3 (8.3)	1.66 (0.08)	65.2 (14.2)

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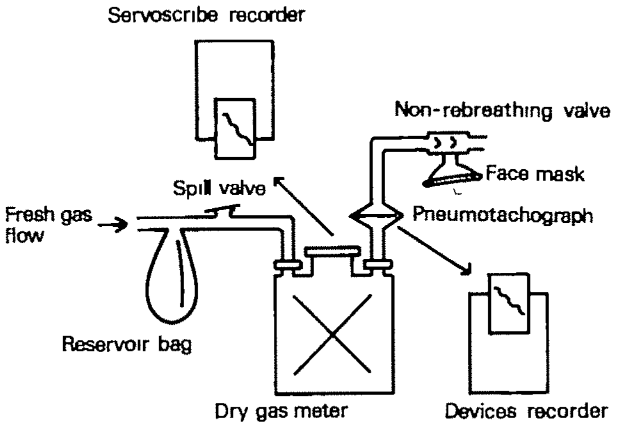

FIG. 1. Diagram of apparatus used.

meter dial had been modified to give an electrical signal that was recorded using a potentiometric recorder (Servoscribe). The differential pressure from the pneumotachograph was measured with a Furness transducer and the flow signal recorded with a heated pen recorder (Devices M2) to allow measurement of inspiratory and expiratory times.

Baseline 5-min recordings of ventilation and flow were obtained once stable anaesthesia was attained. The first dose of the relevant drug (see below) was administered, and a further 5-min recording obtained. This was repeated after the second dose of the drug to assess the possibility of an alteration in response to a second dose as is seen for agonist–antagonist agents such as pentazocine. The drugs (and doses) studied were pethidine 20 mg + 20 mg, meptazinol 20 mg + 20 mg, meptazinol 30 mg + 30 mg and meptazinol 48 mg + 48 mg (groups I–IV, respectively).

Minute volume, tidal volume and ventilatory frequency were measured from the Servoscribe recording. Inspiratory and expiratory times were measured from the pneumotachograph record and mean inspiratory flow rate calculated from the above data. Statistical comparison between and within groups was by Student's *t* test, paired or unpaired, as appropriate.

RESULTS

There were no significant differences between the groups in respect of age, height and weight (table I).

The mean minute volume was not significantly different between the groups throughout the control period and remained steady (fig. 2).

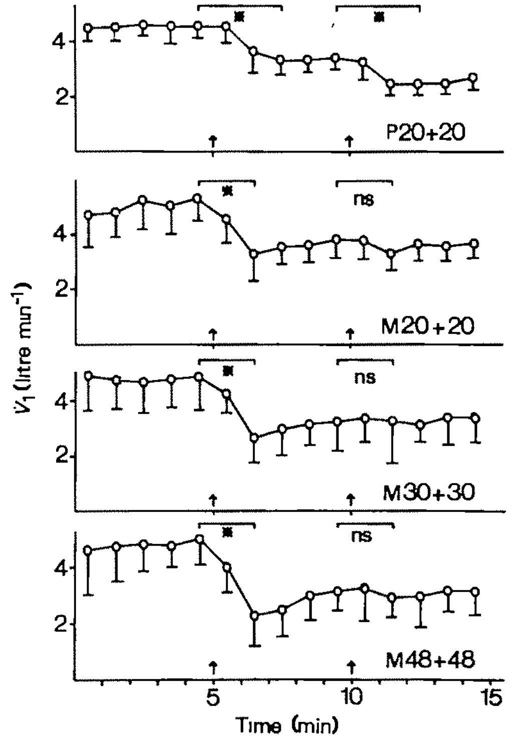

FIG. 2. Changes in mean minute ventilation in the four groups (mean values and SD). P20+20 = Pethidine 20 mg+20 mg; M20+20 = meptazinol 20 mg+20 mg; M30+30 = meptazinol 30 mg+30 mg; M48+48 = meptazinol 48 mg +48 mg. ↑ = Time of administration of drug. *$P < 0.001$.

Following the administration of the first dose of drug there was a significant decrease in minute volume in all groups. The time course of effect on minute volume was maximal at 2 min with meptazinol and 3 min with pethidine. Accordingly, statistical comparison was made between the final control measurement and the mean value of minute ventilation 2 min later in the meptazinol groups and 3 min later in the pethidine group. Following the second dose of drug there was a further significant decrease in minute ventilation after 3 min in the pethidine group, but no effect in any of the meptazinol groups.

Mean ventilatory frequency remained steady throughout the control period and was comparable between groups. After the first dose of drug there was a significant decrease in ventilatory frequency in all groups which plateaued at the end of the 5-min period (fig. 3). The extent of this effect was dose-dependent with meptazinol. After the second dose of drug there were further significant decreases in ventilatory frequency in the pethi-

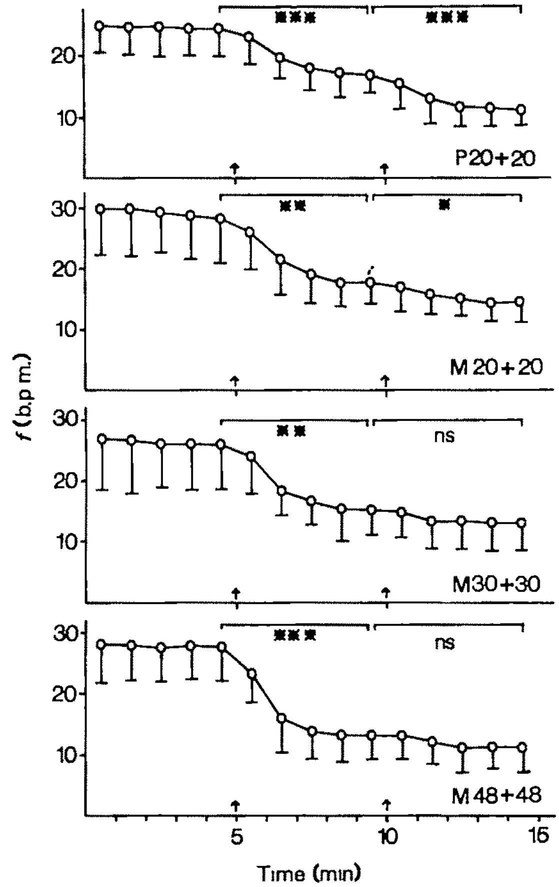

FIG. 3. Changes in mean ventilatory frequency in the four groups (mean values and SD). P20+20 = Pethidine 20 mg+20 mg; M20+20 = meptazinol 20 mg+20 mg; M30+30 = meptazinol 30 mg+30 mg; M48+48 = meptazinol 48 mg+48 mg. ↑ = Time of administration of drug. $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$.

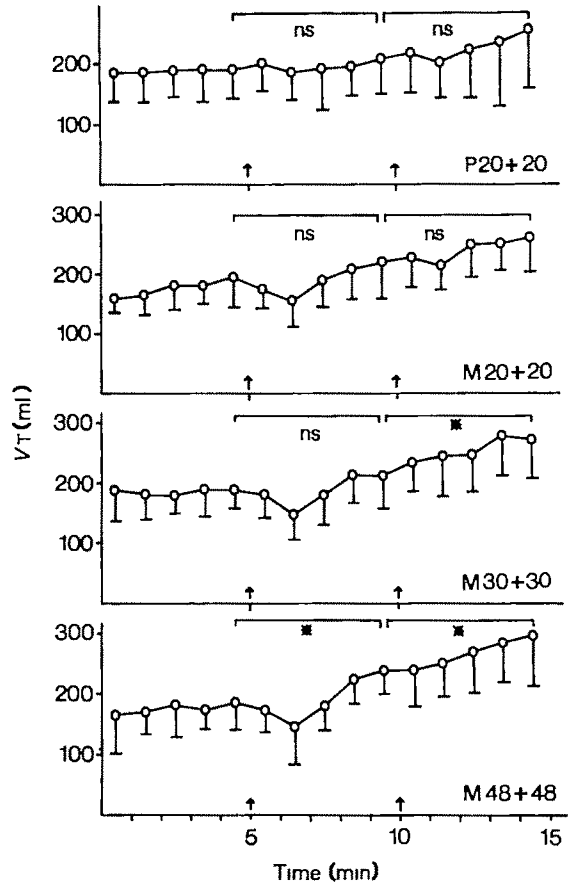

FIG. 4. Changes in mean tidal volume in the four groups (mean values and SD). P20+20 = Pethidine 20 mg+20 mg; M20+20 = meptazinol 20 mg+20 mg; M30+30 = meptazinol 30 mg+30 mg; M48+48 = meptazinol 48 mg+48 mg. ↑ = Time of administration of drug. $^{*}P < 0.05$.

dine, and meptazinol 20 mg, groups. Ventilatory frequency decreased following the second dose of drug in the meptazinol 30 mg and 48 mg groups, but this failed to achieve significance.

Pethidine had no effect on tidal volume (fig. 4). In all three meptazinol groups there was an initial (non-significant) decrease in tidal volume 2 min after the first dose of drug. This was followed by a steady increase in tidal volume, which was significant after the first dose in the meptazinol 48 mg group, and after the second dose in the meptazinol 30 mg and 48 mg groups. Comparison was between the beginning and end of each 5-min period in all cases.

The log dose–response curve of meptazinol against ventilation following a single dose was approximately linear and demonstrated meptazinol 20 mg to be equipotent with pethidine 20 mg (fig. 5). These two groups were therefore considered capable of statistical comparison after the second dose of drug. Before the administration of the second dose there were no significant differences between these two groups in respect of minute ventilation, frequency or tidal volume. After the second dose there was a significant difference in ventilation, although no statistical differences could be demonstrated for tidal volume and frequency between the two groups (fig. 6).

Mean inspiratory time was unaffected by any dose of either drug (fig. 7).

Mean expiratory time was steady in each group throughout the control period. After the injection

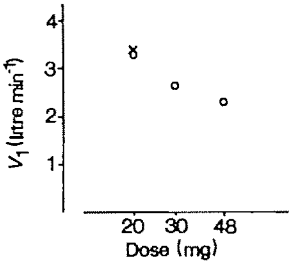

FIG. 5. Mean minute ventilation at the time of maximal depression after a single dose of meptazinol or pethidine (logarithmic scale). ○ = Meptazinol; x = pethidine.

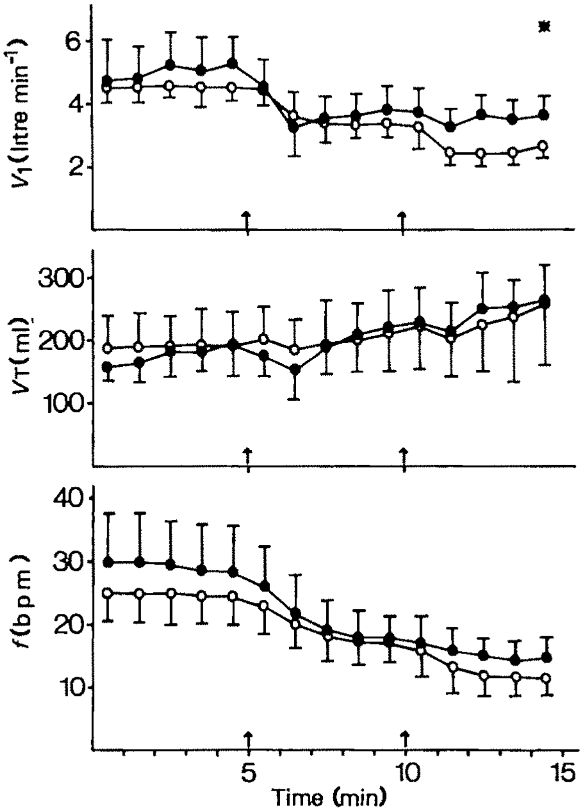

FIG. 6. Changes in mean minute ventilation, ventilatory frequency and tidal volume in the meptazinol 20 mg+20 mg and pethidine 20 mg+20 mg groups (mean values and SD). ● = Meptazinol; ○ = pethidine. ↑ = Time of administration of drug. $*P < 0.01$.

of the first dose of drug there was a significant increase in mean expiratory time in all groups which plateaued by the end of the 5-min period (fig. 8). After injection of the second dose of drug there was a further significant increase in

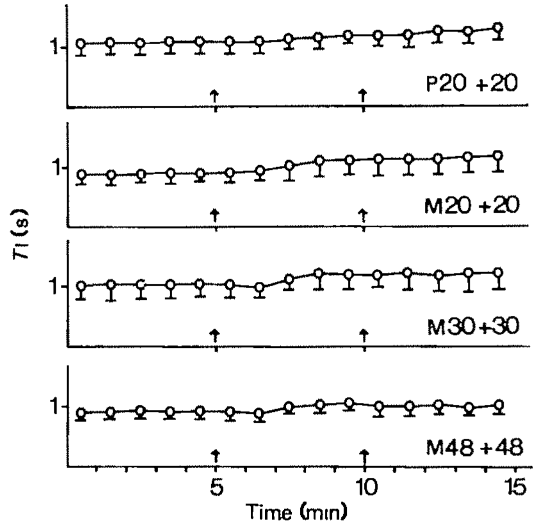

FIG. 7. Changes in mean inspiratory time in the four groups (mean values and SD). P20+20 = Pethidine 20 mg+20 mg; M20+20 = meptazinol 20 mg+20 mg; M30+30 = meptazinol 30 mg+30 mg; M48+48 = meptazinol 48 mg+48 mg. ↑ = Time of administration of drug.

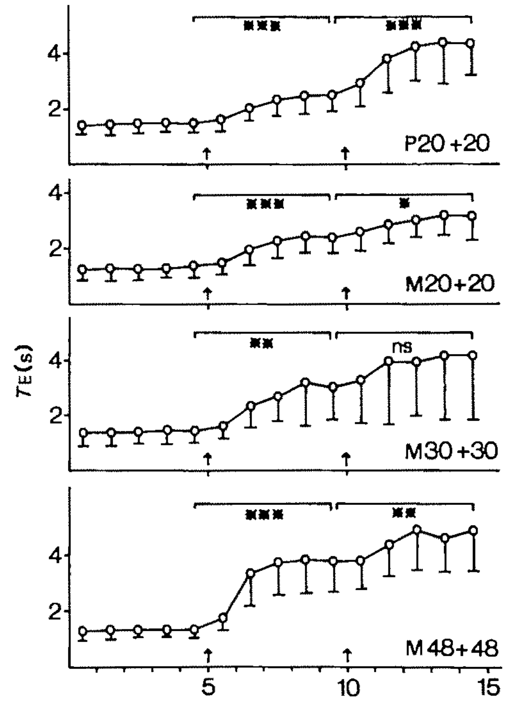

FIG. 8. Changes in mean expiratory time in the four groups (mean values and SD). P20+20 = Pethidine 20 mg+20 mg; M20+20 = meptazinol 20 mg+20 mg; M30+30 = meptazinol 30 mg+30 mg; M48+48 = meptazinol 48 mg+48 mg. ↑ = Time of administration of drug. $*P < 0.05$; $**P < 0.01$; $***P < 0.001$.

expiratory time in all groups except the meptazinol 30 mg group, in which there was a wider scatter of results. The log dose–response curve of meptazinol against expiratory time after a single dose was linear and again demonstrated meptazinol 20 mg to be equipotent with pethidine 20 mg (fig. 9).

Mean inspiratory flow rate remained unchanged after both doses of pethidine. In all three meptazinol groups there was an initial non-significant decrease in mean inspiratory flow rate 2 min after the first dose of drug. This was followed by a steady increase which was significant after the second dose in the 30-mg and 48-mg groups (fig. 10).

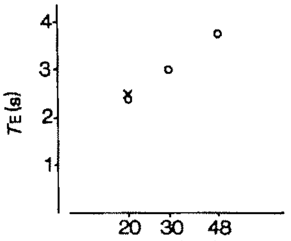

FIG. 9. Mean expiratory time 5 min after a single dose of either meptazinol or pethidine (logarithmic scale). ○ = Meptazinol; x = pethidine.

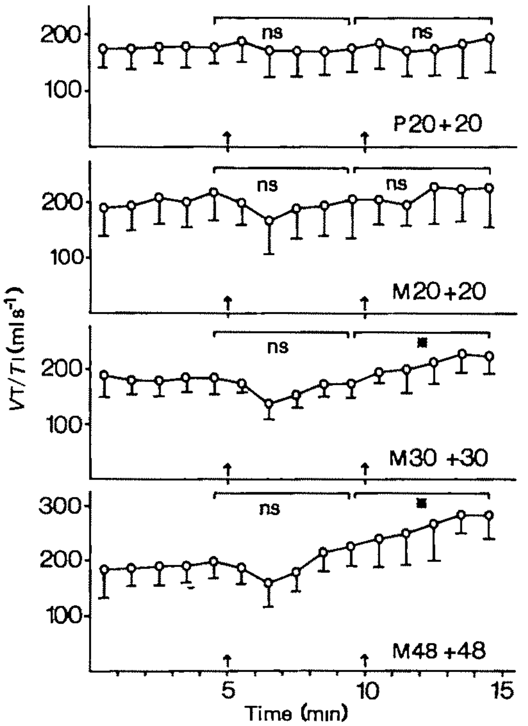

FIG. 10. Changes in mean inspiratory flow rate in the four groups (mean values and SD). P20+20 = Pethidine 20 mg+20 mg; M20+20 = meptazinol 20 mg+20 mg; M30+30 = meptazinol 30 mg+30 mg; M48+48 = meptazinol 48 mg+48 mg. ↑ = Time of administration of drug. $*P < 0.01$.

DISCUSSION

This study has clearly shown meptazinol to have potent effects on ventilation in anaesthetized subjects.

Three doses of meptazinol were studied, encompassing the range of doses reported as equianalgesic to pethidine by other authors (Paymaster, 1977; Slattery et al., 1981). We constructed log dose–response curves of the effects of meptazinol on ventilation and found that the potency ratio, at the 20-mg dose, relative to pethidine, was 1:1. Both drugs have marked effects on ventilation, but there are striking differences in their behaviour after repeated injections. Consequently, it was only possible to compare potency after a single injection. In this respect the actions of meptazinol are very similar to those of another agonist–antagonist drug, namely pentazocine (Davie, Scott and Stephen, 1970). However, meptazinol and pentazocine have been shown to differ in their effects on ventilation in conscious volunteers (Jordan et al., 1979) and the "ceiling effect" seen with pentazocine is probably not the effect that is being seen with meptazinol, as will be discussed later.

In this study the basic indices of breathing, namely ventilatory drive and timing (Clark and von Euler, 1972; Gautier, 1980) were assessed by calculating V_T/T_I and measuring inspiratory and expiratory timing intervals.

In common with other opioids (Rigg and Rondi, 1981; Drummond, 1983) the predominant effect of meptazinol and pethidine was on timing, resulting in a decrease in ventilatory frequency entirely as a result of a prolongation of expiration. These effects are much more evident in patients during anaesthesia than in the conscious state. Although other changes would be occurring after administration of the drug, it would be unlikely for these changes to contribute to the effects on timing. The alveolar concentration of halothane would be decreasing and alveolar P_{CO_2} increasing because of the depression of ventilation and these changes would be occurring at different rates. However, changes in the depth of anaesthesia with volatile agents do not appear to have a marked effect on timing (Drummond, 1983; Murat et al., 1985) and neither does an increasing Pa_{CO_2} in the early stages (Drummond, 1984).

Ventilatory drive, as measured by V_T/T_I, underwent an initial non-significant decrease 2 min after all first doses of meptazinol. This contributed to the early depression of minute ventilation and is similar to fentanyl, which has effects on timing and drive (Drummond, 1983). With fentanyl the effect on timing is more marked and takes longer to develop than the effect on drive, which occurs within 1–2 min. Following the initial depression of V_T/T_I after meptazinol there was a steady increase. This achieved significance after the second doses in the 30-mg and 48-mg groups and also accounts for the increases in tidal volume. This increase in ventilatory drive is presumably the result of increasing values of Pa_{CO_2}. In the presence of meptazinol, in contrast to pethidine, an increase in ventilation can occur after minute ventilation has been reduced by changes in ventilatory frequency caused by altered timing intervals. This is substantiated by the work of Jordan and colleagues (1979) and is consistent with their findings that the slope of the ventilatory response to rebreathing carbon dioxide is largely unaffected by meptazinol. This is in contrast to their finding that pentazocine has marked effects on the slope of the ventilatory response to rebreathing carbon dioxide. A ceiling effect with pentazocine can be seen after successive doses in the same patient (Davie, Scott and Stephen, 1970). In conjunction with this lack of effect on frequency and tidal volume following a second dose of pentazocine, Jordan and colleagues' findings would suggest that the ceiling effect seen with pentazocine is not a result of the compensatory mechanisms that come into play following repeated doses of meptazinol.

The depressant effect of drugs may be caused by a predominant effect on only one of the basic indices of breathing. For example, volatile anaesthetics predominantly influence inspiratory flow (Drummond, 1983; Murat et al., 1985), whereas opioids and ketamine predominantly influence timing (Drummond, 1983; Jaspar et al., 1983). Compensation may occur, through the effects of carbon dioxide retention, but this may lag behind the rate of onset of action of the depressant. In addition, the mechanism of compensation may be different from the manifest depressant effects. In this study the initial effect was a reduction in minute ventilation which was attributable partly to a reduction in tidal volume, but this was followed by an increase in V_T/T_I and tidal volume as T_I/T^{tot} continued to decrease. After oral administration the relatively slow absorption of a drug may allow adequate compensation for its effects, but after i.v. administration compensation may not be achieved rapidly enough for safety. Concurrent administration of other ventilatory depressants such as volatile anaesthetics is a common clinical situation and may influence the margin of safety. Investigations commonly used to assess ventilatory depression may not be relevant for all circumstances in which a drug is used clinically.

Ventilatory depression by meptazinol is predominantly the result of its effects on timing. It may also have a direct depressant effect on the neural mechanisms responsible for "drive", but compensation after ventilatory depression can occur by an increase in inspiratory flow. Although this compensation for ventilatory depression by meptazinol may be greater than with other opioids, it takes some time to develop and patients could possibly become hypoxic in the period immediately following i.v. administration. It should be remembered that the hypoxic drive to ventilation is abolished by volatile agents (Knill and Gelb, 1978) and depressed by opioids (Weil et al., 1975). It has not been ascertained what effect meptazinol has on the ventilatory response to hypoxia, but even with low concentrations of volatile agents the response to hypoxia is markedly reduced.

There is no doubt that i.v. administration of meptazinol during anaesthesia has to be viewed with as much caution as administration of any other opioid.

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MEPTAZINOL FOR POSTOPERATIVE PAIN RELIEF IN MAN

Comparison of Extradural and I.m. Administration

C. VERBORGH, D. VAN DER AUWERA AND F. CAMU

Since Behar and his colleagues (1979) first reported the extradural application of opioid drugs in man, the effectiveness of this technique in treating both acute and chronic pain has been well established (Cousins and Mather, 1984). However, opioid-induced respiratory depression remains a major risk.

Meptazinol is a centrally acting, lipophilic, mixed opioid agonist–antagonist, with analgesic activity in man (Paymaster, 1976; Stephens, Waterfall and Franklin, 1978). Spiegel and Pasternak (1984), using competition and saturation binding studies in animals, showed that the drug had a high affinity for μ_1-receptors in the central nervous system. They demonstrated that, whereas meptazinol had an analgesic potency similar to that of the classical opioids, and this could be reversed by naloxone, its respiratory depressant effects were minimal.

Since meptazinol has been shown to bind to spinal cord structures in animals (Blurton et al., 1982), it has the potential for an analgesic effect after extradural administration. Any potentially depressant effect on the nuclei in the floor of the 4th ventricle should remain minimal because of the μ_1-receptor selectivity of the drug. The clinical use of extradural meptazinol was reported by Budd, Brown and Robson (1983), who found that 90 mg was the most effective dose in the management of chronic pain.

We have investigated the usefulness of this dose of extradural meptazinol for acute postoperative pain relief and compared this technique with the i.m. administration of the same amount of drug to demonstrate any differences in analgesic activity. Since the absorption kinetics after these routes of administration are reported to be comparable (Rowland and Tozer, 1980), we also monitored (in some patients) the plasma concentrations of meptazinol resulting from these treatments.

SUMMARY

The analgesic and cardiorespiratory effects of meptazinol 90 mg, given by the extradural or the i.m. route, were studied in 32 postoperative patients. Plasma meptazinol concentrations were measured in five patients in each treatment group. Evaluation using a linear analogue scale indicated that there were significant differences between the groups in the onset, quality and duration of pain relief, with the extradural route being superior to the i.m. route in each instance. The difference in quality of pain relief was not related to the resultant plasma meptazinol concentrations, which were similar in the two groups. Ventilatory rate was decreased equally in both groups in parallel with pain relief, but no incidence of overt respiratory depression was noted. Meptazinol produced no meaningful changes in measured cardiovascular variables, and side effects were minimal in both groups.

PATIENTS AND METHODS

The study was carried out in 32 adult patients scheduled for abdominal surgery. None had any systemic disease or history of allergy or of hepatic or renal disease. The design of the study was approved by the Ethics Committee of the Faculty of Medicine and all patients gave informed consent. Occasional medication was discontinued

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48 h before surgery. All the patients were premedicated with diazepam 10 mg orally and glycopyrrolate 0.4 mg i.m.

In the operating theatre an i.v. infusion was commenced. In every patient an 18-gauge extradural catheter was inserted through a 17-gauge needle placed at mid-thoracic level (T5–6) for upper abdominal surgery and at low thoracic (T10–11) or upper lumbar level (L1–2) for lower abdominal surgery. After a negative aspiration test for blood and cerebrospinal fluid, the patients were placed in the supine position and anaesthesia was induced with etomidate 0.3 mg kg^{-1}. Pancuronium 0.08 mg kg^{-1} was administered. Anaesthesia was maintained with enflurane or halothane and nitrous oxide in oxygen. No opioids were used, nor were any injections of local anaesthetics given through the extradural catheter. An arterial cannula was inserted for monitoring purposes.

As soon as the patients complained of pain after recovery from anaesthesia, they received either an extradural injection of meptazinol 90 mg diluted in 0.9% NaCl solution 10 ml (group I, $n = 16$) or an i.m. injection of meptazinol 90 mg (group II, $n = 16$) in a randomized manner. The extradural catheter was flushed with an additional 2 ml of physiological saline solution. Heart rate, mean arterial pressure, ventilatory rate, arterial carbon dioxide tension (Pa_{CO_2}) and pain scores, assessed by the patients by means of linear analogue scales (LAS) (Revill et al., 1976), were recorded before and for up to 6 h after injection. Pain intensity and degree of sedation were also assessed by a physician using a categorical score ranging from 0 to 3, increasing score indicating increasing pain or sedation. The injection of the analgesic, and the assessments of pain and sedation, were carried out by different physicians. Upon recurrence of pain, the observations were discontinued and the patient was given extradural morphine hydrochloride.

In five patients in each group blood samples were taken before and 2, 5, 10, 20, 30, 45, 60, 90 and 120 min and at 3, 4, 5 and 6 h after injection. The blood samples were centrifuged and plasma was stored at −20 °C before analysis. Plasma concentrations of meptazinol were determined by HPLC using fluorescence detection, the lower limit of sensitivity being 3 ng ml^{-1} (Frost, 1981). All data are expressed as the mean ±SEM and were analysed using paired and unpaired t tests for parametric data, and Wilcoxon and Mann–Whitney U test for non-parametric data.

RESULTS

Analgesic effect

The two groups were similar with respect to age, weight and height (table I) and the average times between the end of anaesthesia and the administration of meptazinol were comparable (group I: 92±7 min; group II: 94±6 min). After the injection of meptazinol 90 mg, a more marked decrease in pain score occurred (within 5 min) in group I than in group II (after 20 min) (fig. 1). Compared with control values, the decrease in pain score became statistically significant at 2 min in group I and at 5 min in group II. There was a significant difference between the two groups in

TABLE I. *Physical and surgical characteristics of the patients. Mean values ±SEM (range)*

	Group I (extradural)	Group II (i.m.)
Male/Female	9/7	5/11
Age (yr)	54.9±4.0 (21–82)	54.9±3.7 (31–76)
Weight (kg)	71.0±4.2 (43–95)	66.8±3.0 (48–95)
Height (cm)	166.3±2.4 (154–184)	166.3±1.8 (156–178)
Cholecystectomy	8	7
Right colectomy	2	1
Left colectomy	2	2
Sigmoidectomy	1	—
Anterior resection of the rectum	1	2
Subtotal gastrectomy	1	—
Selective vagotomy	—	2
Splenectomy	1	—
Hysterectomy	—	2
Total	16	16

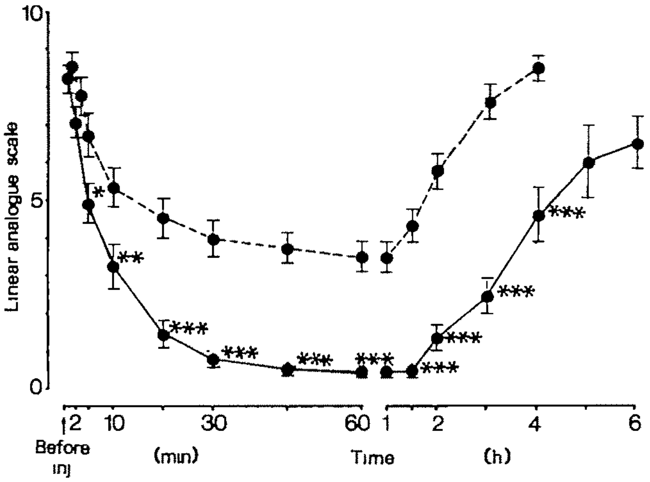

FIG. 1. Effect of meptazinol 90 mg on analogue scale ratings (LAS) after i.m. (—) and extradural (——) administration (mean ± SEM). Differences between groups: $^{*}P < 0.01$; $^{**}P < 0.005$; $^{***}P < 0.001$ (Mann–Whitney U test).

TABLE II. *Frequency distribution of sedation scores*

	Group I (n = 16) (extradural)				Group II (n = 16) (i.m.)			
Sedation score:	0	1	2	3	0	1	2	3
Before	7	9	0	0	1	9	6	0
At 10 min	2	9	5	0	1	9	6	0
At 30 min	0	10	6	0	0	9	7	0
At 60 min	1	10	5	0	0	11	5	0

the quality of pain relief (assessed by the linear analogue scale) at 5 min and this lasted for 4 h. In the extradural group no segmental distribution of analgesia was observed, nor was there any difference in duration or quality of analgesia whether meptazinol was injected at the thoracic or the lumbar level. The duration of analgesia, taken as the time the LAS figure remained less than 5, was 5.06 ± 0.38 h (range 3–7) in group I, and 3.16 ± 0.27 h (range 1.5–5) in group II ($P < 0.001$). The mean time to injection of another analgesic was also longer in group I (325 ± 25; range 180–525 min) than in group II (197 ± 15; range 120–300 min) ($P < 0.001$). A close correlation was seen between the changes in the LAS and the observer's rating using the categorical score. Sedation in group I was minimal or absent at the beginning of the period of observation and became slight to moderate within the next 30 min. Initially, the degree of sedation in group II was somewhat greater than in group I, but after 30 min there was no difference between the groups (table II). There were no cases of marked sedation and no other side effects were noted.

Ventilatory and haemodynamic effects

After the injection of meptazinol, ventilatory rates decreased similarly in both groups (fig. 2). Compared with control values, the maximum decrease in ventilatory rate was 25% after 30 min in group I ($P < 0.01$) and 19% after 45 min in group II ($P < 0.01$). There were no cases of overt ventilatory depression as all patients maintained a ventilatory rate of at least 12 b.p.m. A slight increase in Pa_{CO_2} occurred after 1 h in both groups (fig. 3). The maximum decrease in heart rate was 9% after 10 min ($P < 0.01$) in group I and 8% after 10 min in group II ($P < 0.02$). Mean arterial pressure decreased by 10% after 20 min ($P < 0.01$) in group I and 3% after 45 min in group II (ns).

Plasma concentrations of meptazinol

Absorption of meptazinol from the site of injection to the plasma occurred rapidly. Plasma meptazinol concentrations reached a maximum of 557 ± 68 ng ml^{-1} after 10 min in group I and 409 ± 22 ng ml^{-1} after 5 min in group II. The plasma concentrations decreased similarly over a 6-h period in both groups. Differences between the two groups were not significant (fig. 4).

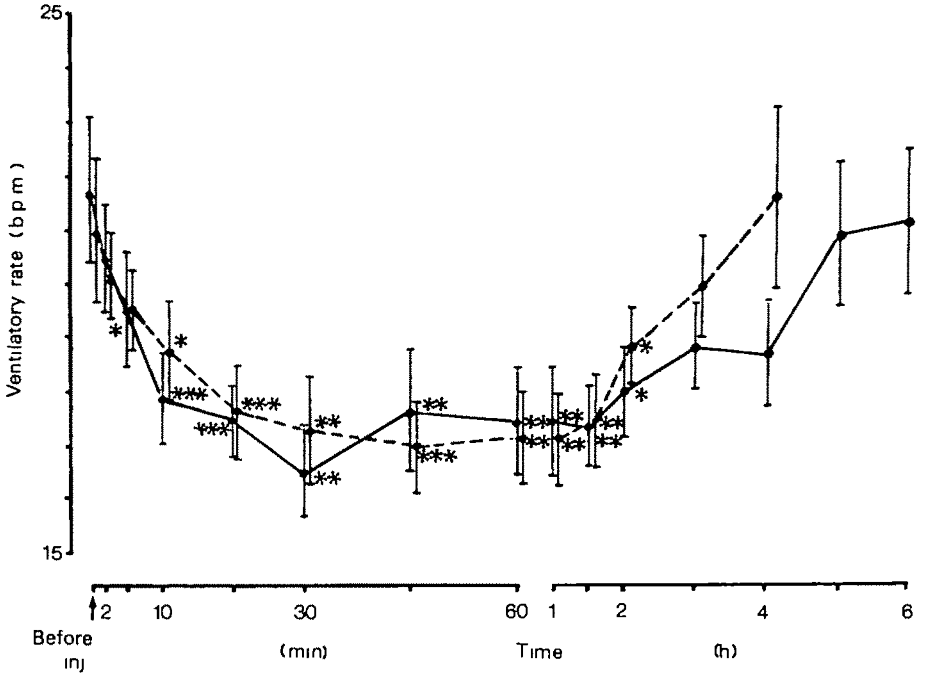

FIG. 2. Change in ventilatory rate after i.m. (—) and extradural (——) administration of meptazinol 90 mg (mean ± SEM). Differences from control: $^*P < 0.05$; $^{**}P < 0.02$; $^{***}P < 0.01$ (Wilcoxon test).

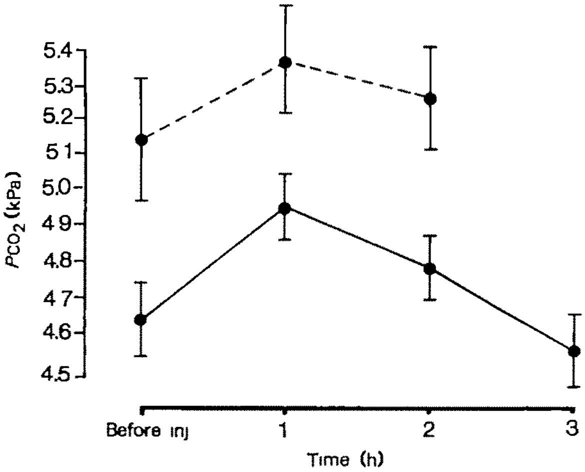

FIG. 3. Effect of i.m. (—) or extradural (——) injection of meptazinol 90 mg on Pa_{CO_2} (mean ± SEM). Differences from control are not significant (Wilcoxon test).

DISCUSSION

A previous study reported successful pain relief with small doses (30 mg) of meptazinol administered extradurally in patients suffering from chronic pain of different aetiologies (Budd, Brown and Robson, 1983). These authors observed a high incidence of side-effects, including nausea and vomiting, dizziness and pain on injection. None of these problems occurred in our patients. Rao and colleagues (1985) reported a similar duration of effect (2 h) with 30 mg or 60 mg of extradural meptazinol after gynaecological surgery and commented on the cardiorespiratory stability. The quality of pain relief provided by both doses was, however, different after 30 and 45 min. Increasing the dose beyond 60 mg might have demonstrated a longer duration of analgesia as reported here.

Extradural injection resulted in higher peak plasma concentrations of meptazinol than i.m. injection; this slight difference, not statistically significant, cannot fully account for the obvious difference in quality of pain relief. Indeed, analgesic activity in group I continued with the same intensity long after the meptazinol plasma concentrations had passed their maxima. At 3 h, plasma concentrations had decreased by a factor of 10, yet a satisfactory degree of pain relief still was evident in the extradural group.

These are arguments for accepting a local spinal site of action of meptazinol as for other lipophilic analgesics. We cannot provide further direct

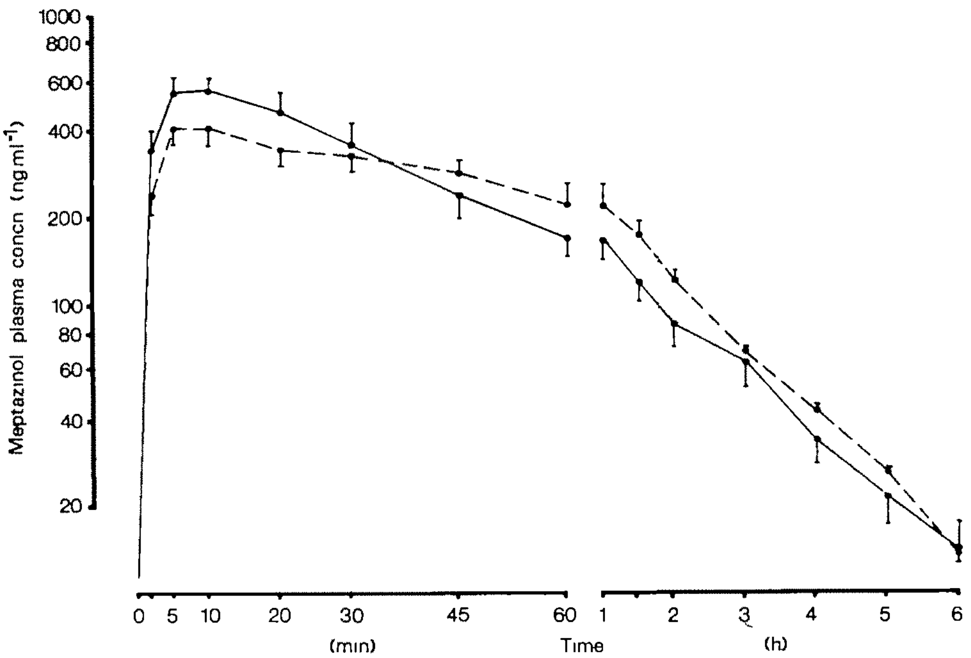

FIG. 4. Time course of the meptazinol plasma concentrations of meptazinol after i.m. (—) or extradural (——) injection of meptazinol 90 mg (mean ± SEM). Differences between the two groups are not significant (Mann–Whitney U test).

evidence that meptazinol shows a high affinity for the μ_1-subtype receptor described by Ling and colleagues (1983); however, we did not encounter overt ventilatory depression, nor did previous workers (Budd, Brown and Robson, 1983). Possibly, the slight decrease in ventilatory rate may have been caused by the absence of painful stimuli. Studies on the relation between meptazinol plasma concentrations, ventilatory function and analgesia could clarify this point.

In a double-blind cross-over study comparing the ventilatory effects of equipotent doses of meptazinol, morphine and pentazocine (Jordan et al., 1979), meptazinol 100 mg i.m. did not depress the slope of the ventilatory response to carbon dioxide, but produced a significant increase in end-tidal carbon dioxide tension. Our finding of an increase in Pa_{CO_2} after injection in part confirmed previous reports. Other authors have reported a lack of ventilatory depression and a constant Pa_{CO_2} after meptazinol 100 mg i.m. (Paymaster, 1976, 1977; Verschraegen et al., 1976; Verschraegen and Rolly, 1979). The slight decrease in heart rate and mean arterial pressure to more normal values could also be related to the disappearance of pain. In a recent review (Robson, 1983), cardiovascular stability was reported to be maintained after meptazinol 100 mg i.m., in contrast to the use of meptazinol in anaesthetic doses (Camu and Rucquoi, 1983).

We conclude that meptazinol 90 mg injected extradurally to postoperative patients induced good analgesia within 5 min, and that this lasted for 5 h with minimal sedative effects. Compared with the i.m. route of administration of a similar dose, the extradural administration of meptazinol provided better quality analgesia which was more rapid in onset and of longer duration.

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Br. J. Anaesth. (1987), 59, 1140–1146

DISPOSITION AND PHARMACOKINETICS OF MEPTAZINOL IN THE CSF

Studies after Intrathecal Administration in the Non-Human Primate Erythrocebus patas

A. K. DHIRI, J. SANFORD AND M. G. WYLLIE

SUMMARY

A preliminary study is reported on the kinetics of meptazinol following intrathecal and i.m. administration in the Patas monkey. Following intrathecal administration (single dose of 0.5 mg) at T12/L1, meptazinol rapidly disappeared from the CSF with a $T_{\frac{1}{2}}$ of 35 min. At 240 min after intrathecal injection, most of the meptazinol had been distributed within the spinal tissue near the region of the injection, with minimal amounts reaching the brain (less than 5% of the concentrations present in the lumbar and thoracic tissue). Following i.m. administration (16 mg kg^{-1}) peak concentrations were present in the CSF and plasma within 60 min. Appreciable concentrations persisted in the CSF up to 180 min after i.m. administration. The results would suggest that meptazinol should give rapid but short acting pain relief following intrathecal injection with minimal CNS-related side effects.

In an attempt to prolong analgesia and minimize central depressant effects, there has been much recent interest in the administration of opioid analgesics by the intrathecal route (Yaksh and Rudy, 1976; Winnie, 1980). Although in terms of "efficacy" this practice has achieved considerable success, a disturbing feature has been the appearance of severe respiratory depression in some patients several hours after administration (Glynn et al., 1979; Davies, Cleaver-Tolhurst and James, 1980a, b). The precise mechanism is unknown; however, it is likely that this effect could arise from the passage of drug cranially up the spinal canal, redistribution via the systemic circulation (Covino et al., 1980), or a more localized action on sensory motor neurones caused by the physicochemical properties of the agents (Yaksh and Reddy, 1981).

The novel opioid agonist–antagonist analgesic, meptazinol, has been used by i.v. and i.m. routes in the treatment of severe pain (Cohen et al., 1983; Paymaster, 1983; Robson, 1983). On this basis, and considering the drug's minimal propensity for the production of respiratory depression (Cohen et al., 1983; Paymaster, 1983; Robson, 1983), it has been suggested that meptazinol may offer therapeutic advantages if given by the intrathecal route. Thus, as a prelude to any extensive clinical studies, it was considered important to examine the pharmacokinetics of meptazinol within the cerebrospinal fluid in animals. This report deals with one such study in the primate, *Erythrocebus patas*, selected because of the well documented similarities in cerebrospinal anatomy between man and monkey (Wood et al., 1977). A comparison was made of the disposition of meptazinol following intrathecal and i.m. administration and on the direction of drug movement in the spinal canal of the monkey.

MATERIALS AND METHODS

Compounds

$[^3H]$-Meptazinol specifically tritiated at the ethyl group (custom synthesis for Wyeth Labs, 20–30 µCi mmol^{-1}) and $[^{14}C]$-Sucrose (350 µCi

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mmol^{-1}) were obtained from Radiochemical Centre, Amersham, Bucks. Where appropriate, ratios of unlabelled to labelled meptazinol are given.

Animals

Six female Red Patas monkeys weighing 4.8–5.9 kg, obtained from Shamrock Farms Ltd, Brighton, Sussex, were used. The animals were maintained on Mazuri Primate Diet (SDS Ltd, Witham, Essex) supplemented daily with fresh fruits.

Anaesthesia

Animals were fasted overnight for a period of up to 18 h before anaesthesia, but were allowed free access to water. Anaesthesia was induced by an i.v. injection of Althesin ("Saffan", Glaxovet, Greenford, UK.) via an indwelling 18-gauge venous cannula (British Viggo, Swindon, UK.), which had previously been placed in the recurrent tarsal vein on the posterolateral aspect of either the left or right hind leg. The anaesthetic agent was injected to effect. Following induction of anaesthesia, the trachea was intubated and connected to an anaesthetic machine via a Waters to-and-fro system (used semi-closed) for administration of oxygen at the rate of 50 ml min^{-1}. This technique was adopted to prevent the occurrence of electrocardiographic changes associated with anoxia, which had previously been noted during anaesthesia with Saffan (Dhiri, 1984). The animals were also connected to an ECG recorder (Seimens, Middlesex, U.K.) to monitor heart rate and ECG. Anaesthesia was maintained for the duration of the study by the continuous i.v. infusion of Althesin (0.72 mg min^{-1} of a 1.2 mg ml^{-1} solution in 0.9% w/v saline), the infusion being started 20 min after the induction of anaesthesia.

Drug administration and sample collection

Intrathecal studies. The thoracic 9–10, thoracolumbar 12–1 and lumbar 3–4 intervertebral spaces were tapped using 18-gauge spinal needles (Becton-Dickinson (U.K.) Ltd, Oxford, U.K.). The subarachnoid punctures were performed with the animals lying in left lateral recumbency and the needles were assumed to be in the intrathecal space when clear fluid was seen in the hub of the needles. CSF samples (0.25–0.75 ml) were collected in clear plastic vials and stored on dry ice.

As a prelude to the main investigation, a study in a single animal was undertaken in an attempt to determine the direction of CSF flow within the spinal canal. [^{14}C]-Sucrose (1 μCi ml^{-1}) 100 μl was injected to one monkey (463) at the T12/L1 intervertebral space and the spinal needle withdrawn. Tritiated meptazinol 100 μl (concentration of meptazinol solution 5 mg ml^{-1}; unlabelled/labelled ratio 95:5) was injected to three monkeys (465,466,468) at the level of the T12–S1 intervertebral space and the spinal needle withdrawn. The other two spinal needles were left in place and CSF collected every 30 min for up to 240 min.

I.m. studies. Subarachnoid puncture was performed at T12–S1 in four monkeys (464, 465, 466, 467). Tritiated meptazinol 16 mg kg^{-1} (unlabelled/labelled ratio 98.3:1.7) was injected to the quadriceps muscle band of the hind leg opposite to the leg that had been cannulated for the administration of anaesthesia. CSF, and blood samples (from the cannulated leg), were collected every 30 min for up to 240 min.

The animal usage in the various procedures (*vide supra*) is summarized in table I. An interval of 2 weeks was allowed for the two animals which were used for both intrathecal and i.m. studies. This was considered to be sufficient for all the meptazinol to have disappeared from the animals following the first of the procedures (Franklin and Aldridge, 1976).

Measurement of radioactivity. Radioactivity in the samples of CSF and blood was determined by liquid scintillation spectrometry, using a Beckman LS3800 counter, and corrected for quench efficiency. In one monkey (465) various sections of

TABLE I. *Animal usage for each part of the study in Red Patas monkeys*

	Animal No.						
Procedure	463	464	465	466	467	468	Total No.
[^{14}C]-Sucrose intrathecal	+						1
[^{3}H]-Meptazinol intrathecal			+	+		+	3
[^{3}H]-Meptazinol i.m.		+	+	+	+		4

TABLE II. *CSF concentration of [^{14}C]-sucrose following intrathecal administration at the T12–L1 intervertebral space*

Time after dosing (min)	Concentration (nmol ml^{-1}) Lumbar	Thoracic
30	0.92	0.48
60	0.38	0.06
90	0.22	0.03
120	0.11	0.02
180	0.07	0.01

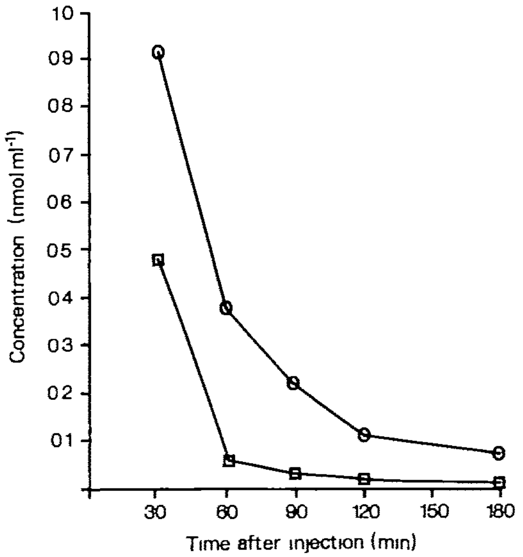

FIG. 1. Decay of [^{14}C]-sucrose in the CSF following intrathecal injection at T12–L1 intervertebral space in the Patas monkey. ○ = Concentration at L3–4, □ = concentration at T9–10.

the brain and spinal cord were homogenized in Tris (50 mmol, pH 7.4) and aliquots taken for measurement of radioactivity by liquid scintillation spectrometry. All values refer to total tritium. No attempt was made to quantify [^{3}H]-meptazinol or [^{3}H]-metabolites. The major metabolite of meptazinol in the monkey is a glucuronic acid conjugate (Franklin and Aldridge, 1976) which is highly hydrophilic, with minimal ability to cross the blood–brain barrier. Thus the radioactivity measured in the CSF is assumed to reflect unchanged meptazinol. On the other hand, the radioactivity measured in the plasma reflects both unchanged drug and its glucuronide conjugate.

RESULTS

Disposition of [^{14}C]-sucrose following intrathecal administration

The results of this study are presented in table II and show that a higher concentration (nmol ml^{-1}) of sucrose was present in lumbar CSF samples than in thoracic samples. Sucrose appears to disappear rapidly from the CSF with a half-life of approximately 30 min (fig. 1).

Disposition of [^{3}H]-meptazinol following intrathecal admininstration

The results are presented in table III. Thoracic CSF samples could only be collected from one of the monkeys up to the 90-min sample, although lumbar samples were readily collected thereafter. This was probably caused by dislodgement of the needle in the thoracic region. An attempt to retap

TABLE III. *CSF concentration of [^{3}H]-meptazinol (measured as total tritium) following intrathecal administration at the T12–L1 intervertebral space*

Time after injection (min)	Concentration (mmol ml^{-1}) Lumbar No. 465	No. 466	No. 468	Mean ± SEM	Thoracic No. 465	No. 466	No. 468	Mean ± SEM
30	1.91	1.36	5.70	2.99±1.4	0.10	0.51	6.27	2.29±2.0
60	1.21	2.13	3.25	2.53±0.7	0.70	0.51	3.06	1.42±0.8
90	0.40	1.04	1.67	1.04±0.4	0.03	0.27	1.65	0.65±0.5
120	0.20	0.76	0.93	0.63±0.2	—	0.20	0.54	0.37±0.2
150	0.10	0.44	0.66	0.40±0.2	—	0.12	0.92	0.52±0.4
180	0.06	0.35	0.50	0.30±0.1	—	0.04	0.46	0.25±0.2
210	0.04	0.24	0.39	0.22±0.1	—	0.03	0.33	0.18±0.2
240	0.04	0.14	0.30	0.16±0.1	—	0.00	0.23	0.12±0.1

TABLE IV. *Concentration of [^{3}H]-meptazinol measured as total tritium in the brain and along different sections of the spinal cord, 240 min after intrathecal administration at the T12–L1 intervertebral space. * Thoracic sample site; † Lumbar sample site*

Samples site	[^{3}H]-Meptazinol (μmol/ml of homogenate)
Cerebellum	5.34
Cerebrum	2.67
Medulla	2.11
Base of brain	11.70
Cervical 4–7	10.00
Thoracic 2–5	8.58
Thoracic 5–10	15.68
Thoracic 10–12*	387.49
Lumbar 1–3†	631.96
Lumbo-sacral	1.44

the intrathecal space was made, but was unsuccessful. The results show that meptazinol also has a decay similar to, but slightly slower than, that of sucrose.

The decay of meptazinol in the CSF is shown in figure 2. The rate of decay from both the lumbar and thoracic regions appear to be the same with a half-life of approximately 35 min. The mean lumbar concentrations are higher than the thoracic concentration and once again, indicate a probable cranio–caudal flow of the CSF.

At the end of the study, concentrations of tritiated meptazinol in the brain and spinal cord of one monkey (465) were assayed. The results of the assay, at various levels of the brain and spinal cord, are presented in table IV. It appears that the majority of the injected material was distributed within the spinal tissue at or near the site of injection.

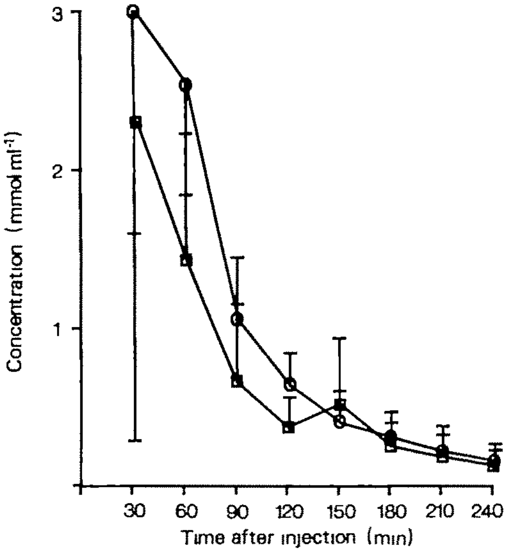

FIG. 2. Decay of meptazinol (measured as total tritium) in the CSF following intrathecal injection at T12–L1 intervertebral space in the Patas monkey. ○ = Concentration at L3–4; □ = concentration at T9–10.

Disposition of meptazinol following i.m. administration

The concentrations of meptazinol (measured as total tritium) in the CSF and in the plasma following i.m. administration are presented in table V. In animals 464 and 465, samples could not be collected at 150 min and only a very small amount (< 0.2 ml) could be collected at 180 min, at which time the study was terminated.

The results indicate that appreciable concentrations of meptazinol were achieved in the CSF

TABLE V. *Concentrations of [^{3}H]-meptazinol measured as total tritium in the CSF and plasma following injection to the hind leg*

Time after injection (min)	Concentration (pmol ml⁻¹)									
	CSF					Plasma				
	Animal No.					Animal No.				
	464	465	466	467	Mean ± SEM	464	465	466	467	Mean ± SEM
30	103.3	109.6	120.1	107.6	110.1 ± 4	362.3	392.7	287.7	219.9	315.7 ± 38
60	280.8	246.8	259.0	221.7	253.3 ± 11	362.2	341.3	436.0	372.5	378.0 ± 20
90	222.8	209.9	254.7	258.7	236.5 ± 12	152.9	158.2	325.4	321.8	239.6 ± 49
120	217.2	239.8	298.9	228.6	246.1 ± 18	138.7	183.4	235.1	206.0	190.8 ± 20
150	—	—	229.4	277.4	253.4 ± 24	—	—	154.4	145.5	151.0 ± 4
180	183.3	188.1	182.1	185.6	184.9 ± 1	117.8	123.2	147.9	138.5	132.0 ± 7
210	—	—	123.8	138.9	131.3 ± 8	—	—	128.9	123.7	126.3 ± 3
240	—	—	128.2	110.0	119.1 ± 9	—	—	93.6	128.1	110.9 ± 17

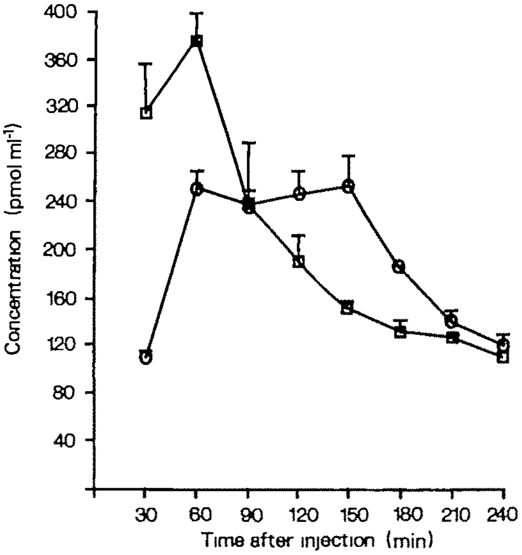

FIG. 3. Concentrations of meptazinol (measured as total tritium) in the CSF (○) and plasma (□) following i.m. administration in the Patas monkey.

within 30 min of i.m. administration. Peak radioactivity in CSF and plasma was achieved at 60 min and 45–67 % of peak plasma radioactivity was present in CSF up to 180 min from the time of administration. Since the radioactivity in CSF reflects mainly unchanged meptazinol and the radioactivity in plasma reflects both unchanged meptazinol and its glucuronide conjugate, it can be assumed that appreciable amounts of meptazinol would persist in the CSF for up to 180 min from the time of administration. Figure 3 illustrates the radioactivity present in the CSF and plasma after i.m. administration.

DISCUSSION

Although the intrathecal administration of opioid analgesics has gained widespread use as an effective means of producing pain relief, there are still many fundamental questions to be addressed. For instance, little is known about the spread of solutions injected to the spinal canal or the diffusion/transport of compounds from the CSF into tissues of the spinal cord. The rate of disappearance of intrathecally injected analgesics and their relative binding to spinal tissue has been shown to depend upon the lipophilicity of the compound (Bullingham, McQuay and Moore, 1982; Camporesi and Redick, 1983; Cousins and Mather, 1984). Thus highly charged lipophilic compounds such as fentanyl and pethidine (heptane:water partition coefficients of 19.35 and 3.4, respectively, at pH 7.4) have been shown to disappear rapidly from CSF and bind to spinal tissue. In contrast, morphine, which is hydrophilic (heptane:water coefficient of < 0.00001 at pH 7.4), tends to persist for a much longer period in the CSF. Meptazinol (heptane:water partition coefficient of 0.48 at pH 8) has a lipophilicity intermediate between those of morphine and pethidine, and would therefore be expected to persist in CSF for a shorter period than morphine. The results of the present study appear to be consistent with this prediction, since the $T_{\frac{1}{2}}$ of meptazinol, after intrathecal injection, was relatively short (about 35 min); yet in the one animal sacrificed, concentrations of 387–632 μmol ml^{-1} were apparent in homogenates of spinal tissues 4 h after intrathecal administration. This persistence is apparently at variance with the short duration of analgesia seen following the extradural administration of meptazinol in clinical studies (Rao et al., 1985). It seems possible that meptazinol, when taken up by spinal tissue, may not be available for interaction with opioid receptors, although the tissue concentrations are well in excess of those required to activate these receptors (Pasternak et al., 1983).

The other pertinent factor affecting distribution of intrathecally injected analgesics is the spread of the injected agents within the CSF. The question of particular relevance is whether the spread is predominantly cranial or caudal to the site of injection, since a cephalad spread has been incriminated in causing the severe respiratory depression seen several hours after intrathecal administration of morphine in man (Davies, Cleaver-Tolhurst and James, 1980a, b). Previous studies in monkeys (Reiselbach et al., 1962) have shown that the volume of injected material is an important factor determining the extent of distribution from the lumbar sac. When this volume was 10 % or more of the total volume of CSF, then significant concentrations of the injected solution were present in the basal cisterns. In the present study, the monkeys weighed 4.8–5.9 kg and, hence, would have had CSF volumes ranging from 12 to 16 ml (Reiselbach et al., 1962). With an injectate volume of 0.1 ml, representing only about 0.6–1 % of the total CSF volume, this factor would be insignificant. Although some workers (Davies, Cleaver-Tolhurst and James, 1980a, b; Gjessing and Tomlin, 1981) have suggested that, in man, intrathecally injected morphine forms a reservoir within the CSF and spreads cephalad to the basal cistern and the brain, extensive work in animals (Yaksh and Rudy, 1976; Yaksh, 1978; Yaksh and Reddy, 1981) has failed to show this. Camporesi and Redick (1983) meanwhile suggest that, in man, coughing or straining may cause cephalad spread of intrathecally administered analgesics. The results of the present study tend to support the work of Yaksh (1978) and to indicate a possible cranial–caudal flow of intrathecally injected agents. This suggestion is based on the finding that in one monkey, in which a non-metabolizable extracellular water marker ([^{14}C]-sucrose) was injected at T12–L1, higher concentrations were obtained at L3–4 than at the T9–10 sample site. A similar mean concentration difference was seen in monkeys injected intrathecally with [^{3}H]-meptazinol. However, with sample volumes of 0.25–0.75 ml, the apparent cranio–caudal flow may be an experimental artefact; removal of fluid from the lumbar region could have resulted in a flow of undiluted agent down the cord, whereas simultaneous removal from the thoracic region could have led to caudal diffusion and dilution with CSF from the cisterna magna. However, it remains that there was a greater concentration of meptazinol within the cord tissue near the injection site, with less than 5% of that concentration being present in cord tissue cranial to this site and even lower concentrations achieved within the brain. It is likely, therefore, that little or no meptazinol would reach the brain by either cephalad diffusion or systemic redistribution.

The study on the disposition of meptazinol following i.m. administration showed that peak concentrations of meptazinol were attained in the CSF and plasma at about the same time. This is consistent with rapid equilibration across the blood–brain barrier. In addition, between 49 and 67% of peak plasma concentrations were present within the CSF up to 180 min after i.m. administration.

CONCLUSION

On the basis of these primate studies, meptazinol injected intrathecally should give rapid but short acting pain relief with minimal side effects such as a CNS depression. The results of a preliminary study of extradurally administered meptazinol in the control of pain following major abdominal surgery (Rao et al., 1985) have, indeed, shown that pain relief is achieved relatively quickly, but is of short duration.

Although this study did not give a clear indication of the direction of spread of intrathecally administered agents, it did show that a variety of factors may contribute to this. It is likely that agents such as morphine that persist in CSF can move, either actively or passively, cephalad to the brain from the point of intrathecal injection along a concentration gradient, or because of mechanical movement of the subject. A similar hypothesis has been proposed for the distribution of morphine in CSF following intrathecal administration in sheep (Payne and Inturrisi, 1985). However, with more lipophilic compounds, including meptazinol, minimal cephalad flow should occur because of a greater binding to spinal tissue with relatively low concentrations present within the CSF.

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ANALGESIC AND RESPIRATORY EFFECTS OF EXTRADURAL SUFENTANIL IN VOLUNTEERS AND THE INFLUENCE OF ADRENALINE AS AN ADJUVANT

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SUMMARY

The effects of extradural sufentanil 50 μg were investigated in 10 normal volunteers. Eight of these were studied at a second session when adrenaline 1:200000 was added to the sufentanil. Well-defined segmental analgesia developed rapidly after plain sufentanil and lasted approximately 3 h. Respiration was depressed for about the same period and was greatest in the first 2 h, as shown by a 15% increase in PE_{CO_2}*, while the slope and* VE_{60} *of the carbon dioxide response curve were depressed by 45% and 55%, respectively. Moderate drowsiness occurred in most subjects, while other side effects of itching, nausea and urinary retention occurred less frequently and were not severe. Addition of adrenaline 1:200000 intensified segmental analgesia and prolonged duration to 5 h, while side effects were lessened. It is concluded that extradural sufentanil shows considerable promise for clinical use, and that the risk: benefit ratio is improved by adding adrenaline 1:200000.*

Intraspinal narcotics were introduced in the hope that powerful segmental analgesia could be achieved at the level of the spinal cord, without depression of the respiratory neurones in the medulla and pons (Yaksh and Rudy, 1976). Subsequent work in animals and man has shown that rostral spread in the cerebrospinal fluid (CSF) is an inescapable element of the pharmacokinetics of extradural and subarachnoid narcotics. Poorly lipid-soluble agents such as morphine, spread widely in the CSF and then gradually penetrate the surface of the neuraxis with which they come in contact. Thus morphine shows a characteristically slow onset of analgesia and a tendency to cause dangerous respiratory depression many hours after administration (Bromage et al., 1982; Camporesi et al., 1983).

In contrast, a narcotic such as sufentanil, which is approximately 1000 times more lipid-soluble than morphine, might be expected to show very different pharmacokinetics, and more favourable pharmacodynamics, based on a very rapid passage from CSF to cord lipids, with a proportionally lesser degree of rostral spread in the CSF (Cousins and Mather, 1984). Sufentanil is considered to be seven to 10 times more potent than fentanyl when given i.v. (Niemegeers et al., 1976) and so, in man, extradural doses of 10–20 μg might be expected to give results equivalent to those of extradural fentanyl in the dose range 70–100 μg. However, Donadoni and colleagues (1985) reported that 25 μg of extradural sufentanil failed to provide satisfactory clinical analgesia, although 50 μg was followed by good pain relief for 5–6 h without apparent respiratory depression.

The present study of extradural sufentanil in healthy volunteers was designed to answer four questions:

(1) Is effective analgesia produced by an extradural dose of sufentanil 50 μg?
(2) Are any appreciable respiratory or other side effects associated with such a dose?
(3) Is the analgesia segmental in distribution?
(4) Does adrenaline 1:200000, as an adjuvant, have an appreciable effect on either analgesia or any unwanted side effects?

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SUBJECTS AND METHODS

Ten healthy, male volunteers between the ages of 23 and 35 yr were studied in sessions lasting 10–12 h, after written consent and institutional approval. Subjects fasted for 12 h and reclined comfortably in a 20° head-up position. A 16-gauge cannula was inserted to a suitable vein to permit fluid administration and blood sampling. Following a series of control measurements, an extradural catheter was inserted at the 2nd or 3rd lumbar space and correct catheter placement was validated by a preliminary dose of 2% chloroprocaine 10 ml. Thirty minutes after complete regression of the chloroprocaine block, sufentanil 50 μg, made up to a volume of 10 ml with normal saline, was injected through the extradural catheter, and the catheter and attached micropore filter (0.2-μm pore-size) were flushed with 1.5 ml of saline. Plain sufentanil was injected at the first session. Eight of the 10 subjects returned for a second session 2–3 months later, when adrenaline 1:200000 (5 μg ml^{-1}) was added to the same dose and volume of sufentanil. All subjects attended a pre-trial session on the day before the first test session, in order to familiarize themselves with the tests and the apparatus, and to lessen any chances of experimental error arising from anxiety or misunderstanding.

The following tests were performed in a resting control period, and then at intervals for 6–8 h after the extradural injection of sufentanil.

Blood sampling

Venous blood samples were drawn from a large forearm vein at 2, 5, 10, 20, 30 and 60 min, and then hourly for 6 h. Ten millilitre of blood was drawn into heparinized syringes and centrifuged at 1100 rev min^{-1} for 10 min. The supernatant plasma was analysed (for sufentanil concentration) by radioimmunoassay. The assay has a lower limit of detection of 0.1 ng ml^{-1} and an accuracy of ±12%.

Algesimetry

Periosteal pressure was applied over forehead, sternum and the anterior surface of the tibia using a calibrated, spring-loaded steel rod of 32 mm^2 cross-sectional area (Bromage, Camporesi and Leslie, 1980). Increasing pressure was applied steadily over each measurement area at the rate of 0.5 kg s^{-1} and the subjects were instructed to say "stop" as soon as the pressure became painful. Three consecutive readings were taken at each site and the average recorded. A fresh adjacent pressure site was taken for successive readings, to minimize tissue bruising and resultant changes in sensitivity.

The Cold Pressor Response Test (CPRT) was measured in hand and foot as described previously (Bromage, Camporesi and Leslie, 1980). The extremity was immersed in ice-water for 2 min while arterial pressure was measured every 30 s by cuff and auscultation in the opposite arm. The pressor response was taken to be the arithmetic mean of the systolic and diastolic arterial pressures measured at 60, 90 and 120 s of immersion, and expressed as a percentage change from the pre-immersion mean. The limb was then rewarmed on a heating blanket and between tests the arterial pressure was allowed to subside to control baseline readings. Cold pressor responses in hand and foot were measured before extradural injection, at 30 min, 60 min and then hourly for 7 h after the extradural administration of sufentanil. Subjects were instructed to record the degree of pain experienced by ice-water immersion on a linear analogue scale of 0–10 cm, where 0 was no pain and 10 the worst imaginable.

Respiratory sensitivity to carbon dioxide

Respiratory depression was assessed by measurements of end-tidal carbon dioxide partial pressure, and by carbon dioxide response curves using a modification of Read's rebreathing method (Camporesi et al., 1983). Subjects breathed through a mouthpiece and nose-clip system into a 9-litre reservoir charged with 5% carbon dioxide in oxygen, until the partial pressure of expired carbon dioxide reached 7.33 kPa. Expired gas was extracted at the mouthpiece at the rate of 200 ml min^{-1} and returned to the reservoir system. Expired carbon dioxide and ventilatory volume were measured on a breath-by-breath basis, using a Beckman infra-red carbon dioxide analyser and a Fleisch pneumotachograph integrated for volume. The volume of each breath and partial pressure of end-expired carbon dioxide were displayed on an Apple II microcomputer screen, stored on floppy discs and printed out at the end of each rebreathing run, together with the equation for the line of the carbon dioxide response curve, calculated by the sum of least squares, and the $\dot{V}E_{50}$ (minute ventilation when end-expired carbon dioxide = 50 mm Hg) (Sherrill and Swanson, 1986).

Four control carbon dioxide response curves were measured before extradural injection and then at 10 min, 45 min, 90 min and thereafter hourly for 6.5 h after administration of the sufentanil. Dermatome levels of hypalgesia to ice and pin scratch were measured at frequent intervals after the extradural injection of sufentanil. Side effects of pruritus, somnolence, nausea and vomiting were also noted.

Statistical analysis

All results were expressed as percentage changes from control. To take advantage of the paired data structure, statistical comparisons between sufentanil, and sufentanil plus adrenaline, were made excluding the two subjects who did not return for the adrenaline session. The statistical procedure used is based on a randomization analysis of randomized block design that has been extended to growth and response curves (Zerbe, 1979a). This is a non-parametric test that permits comparison of several pre-specified time intervals chosen by the investigators. To test for significant differences at these intervals, we used the approximate P values as determined by the standard F distribution with the degrees of freedom as suggested by Zerbe (1979b).

Non-respiratory side effects such as pruritus, nausea, vomiting, somnolence and urinary retention were compared using the chi-squared test.

An estimate or risk:benefit ratio following extradural narcotics may be made by setting arbitrary limits for clinically useful analgesia and for acceptable respiratory risk. Cartwright and his colleagues (1983) found that 50% reduction of the carbon dioxide response curve was associated with a Pa_{CO_2} of 45 mm Hg, which they chose to represent the border of critical respiratory depression, and for the purpose of this study we have selected the same arbitrary index of impending respiratory depression. The arbitrary lower limit of analgesic efficacy has been estimated at 50% depression of CPRT, since earlier studies with extradural morphine indicated this to be approximately equivalent to adequate analgesia for relief of postoperative lower abdominal pain, while 75% depression of CPRT was equivalent to adequate analgesia for upper abdominal pain. Individual post-drug data points for depression of the carbon dioxide response slope were plotted against this arbitrary grid of 50% depression of CPRT and 50% depression of carbon dioxide response, to obtain 2 × 2 tables of four risk–benefit groups: 1 = safe; 2 = unsafe; 3 = effective; 4 = ineffective. The Mantel and Haenzel chi-square test was applied to these data to distinguish the effects of sufentanil from those of sufentanil with adrenaline.

RESULTS

Blood concentrations of sufentanil

Circulating sufentanil was detected in only five of the 10 subjects receiving the plain solution and in four of the eight subjects receiving the adrenaline-containing solution. Average blood concentrations were low and evanescent (table I). The plain solution showed a peak at 2 min, but no drug was detectable after 30 min. The adrenaline solution peaked at 5 min and traces persisted until 120 min. However, these differences were not statistically significant at any time.

Segmental hypalgesia

Segmental hypalgesia to ice and pin-prick developed rapidly—within 15 min of the injection of sufentanil, but appeared sooner after sufentanil with adrenaline (three subjects within 5 min) and extended to between T11 and T9. Upper levels

TABLE I. *Average concentrations of sufentanil in venous blood (ng ml^{-1}) after lumbar extradural injection of sufentanil 50 μg plain or with adrenaline 1:200000 (means ± SD). nd = Not detectable; ns = no significant difference*

	Time (min)						
	2	5	10	20	30	60	120
Plain sufentanil (n = 10)	1.47 (±2.78)	0.044 (±0.09)	0.04 (±0.01)	0.03 (±0.09)	0.03 (±0.09)	nd	nd
Sufentanil + adrenaline (n = 8)	0.04 (±0.08) ns	0.167 (±0.31) ns	0.08 (±0.12) ns	0.05 (±0.07) ns	0.05 (±0.09) ns	0.05 (±0.11)	0.03 (±0.08)

of sensory modulation extended to T9 ± 1 with sufentanil plus adrenaline and to T10 ± 1 with the plain solution. The upper level of hypalgesia remained constant for each subject and did not spread rostrally with either plain sufentanil or sufentanil with adrenaline.

Subjective analgesia

Linear analogue estimate of CPRT pain. All subjects complained of moderate to severe pain during ice-water immersion of an extremity. The average control scores on the linear analogue scale of 0 (no pain) to 10 (most severe pain imaginable) were 6.9 ± 0.31 cm for the hand, and 7.1 ± 0.29 cm for the foot. Profound subjective analgesia occurred in the foot, with a 70–90% depression lasting 1.25 h after plain sufentanil and 2 h after sufentanil with adrenaline (fig. 1). Sufentanil with adrenaline caused very little relief in the hand, but plain sufentanil produced a 50% reduction of linear analogue score for about 1.5 h, probably reflecting a greater degree of vascular uptake and systemic analgesia when adrenaline was omitted.

Periosteal pressure. The average control tolerances for periosteal pressure were 97.8 ± 8.9 g mm^{-2} for forehead, 98.4 ± 8.0 g mm^{-2} for sternum and 138.1 ± 8.8 g mm^{-2} for tibia. Tolerance to periosteal press pressure was increased most in the leg and least in the forehead (fig. 2A, B).

The forehead showed a very slight increase in tolerance in the range 10–20% for 3 h after plain sufentanil and 10–30% after sufentanil with adrenaline. Analgesia in the tibia was most intense during the first 1.5 h, with increased tolerance ranging from 40 to 50% for plain sufentanil and 55 to 85% for sufentanil with adrenaline.

Cold Pressor Response Test. The mean control hypertensive responsive to ice-water immersion of the hand was 36.8 ± 2.03 (SEM)% above resting arterial pressure and 33.9 ± 1.73% above resting values for the foot. Depression of cold pressor response after extradural sufentanil with adrenaline was greater in the foot than in the hand, and greatest when sufentanil with adrenaline was administered (fig. 3). It can be seen that the curves for foot and hand are more widely separated when sufentanil with adrenaline was given ($P = 0.0006$) than with sufentanil alone ($P = 0.014$), and a profound depression of CPRT in the foot to 70–85% below control persisted for 5 h after sufentanil with adrenaline.

Ventilation

In Denver, at an altitude of 1603 m and a barometric pressure of 84.0 kPa, $P\text{E}'_{CO_2}$ is set lower than at sea level; in this series the average resting control value was 4.41 ± 0.09 kPa. End-tidal $P\text{CO}_2$ increased rapidly and significantly to about 15% above control during the first 2 h after plain sufentanil and then declined to 8.5% above control by the 7th hour. On the other hand, sufentanil with adrenaline was followed by a

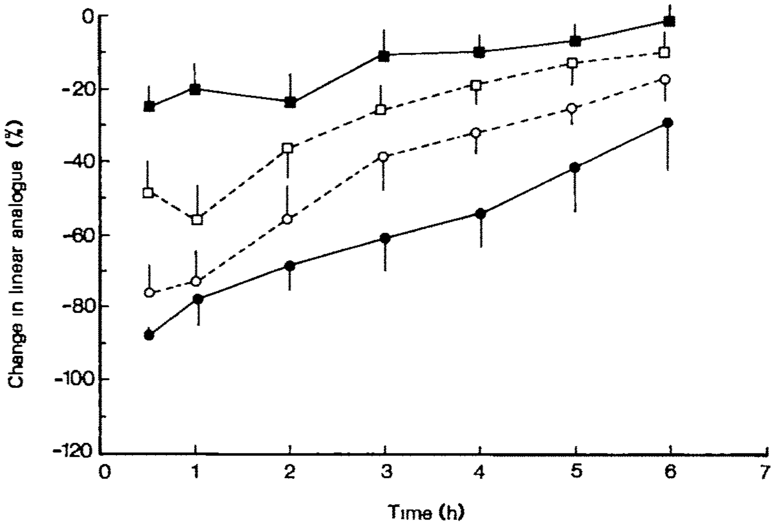

FIG. 1. Subjective analgesia from extradural sufentanil 50 µg. Percentage reduction of linear analogue score in hand and foot after extradural sufentanil 50 µg (means ± SEM). Plain sufentanil: □ = hand, ○ = foot; sufentanil + adrenaline: ■ = hand, ● = foot.

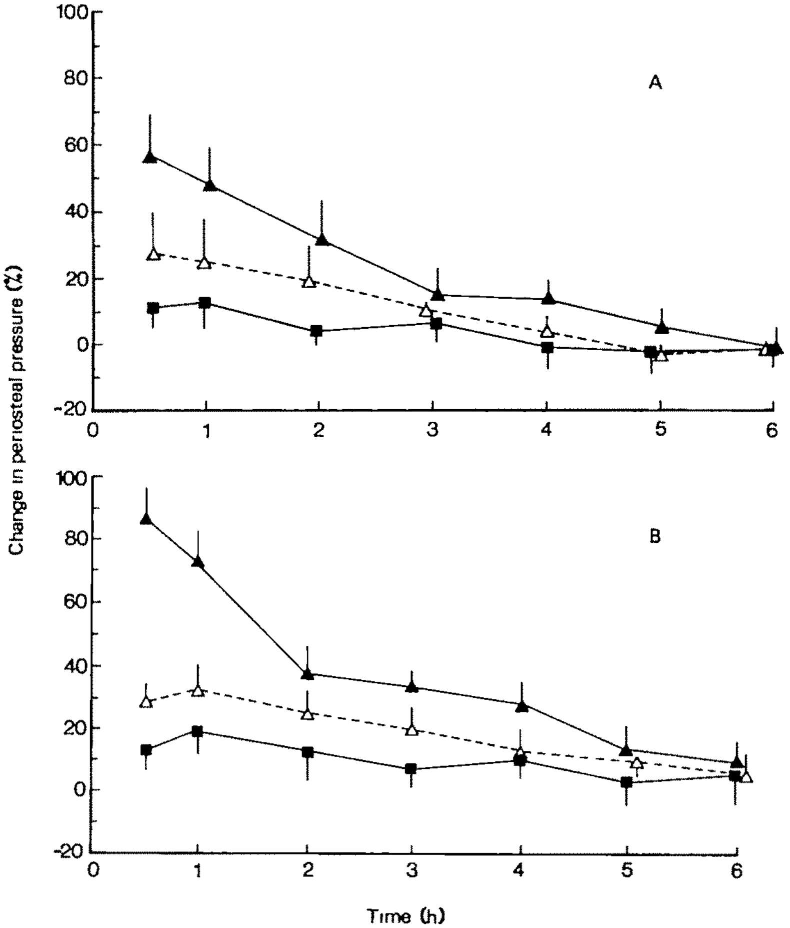

FIG. 2. Percentage change of tolerance to periosteal pressure over forehead, sternum and tibia after extradural sufentanil 50 µg (means ± SEM). A: Plain sufentanil. B: Sufentanil+adrenaline 1:200000. ■ = Forehead; △ = sternum; ▲ = tibia.

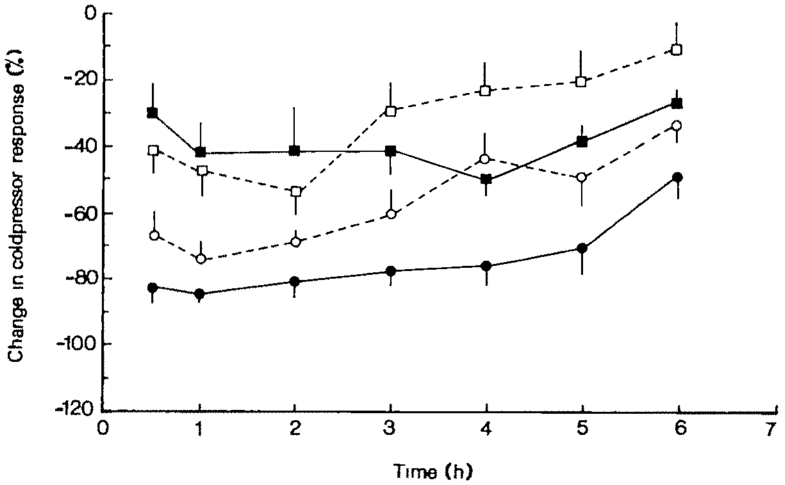

FIG. 3. Percentage reduction of cold pressor response in hand and foot after extradural sufentanil 50 µg (means ± SEM). Plain sufentanil: □ = hand, ○ = foot; sufentanil+adrenaline: ■ = hand, ● = foot.

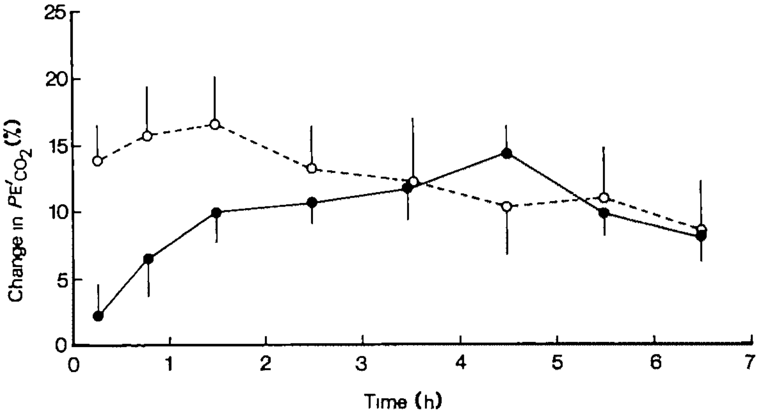

FIG. 4. Percentage change of resting $P\text{E}'_{\text{CO}_2}$ after extradural sufentanil 50 µg (means ± SEM). ○ = Plain sufentanil; ● = sufentanil + adrenaline.

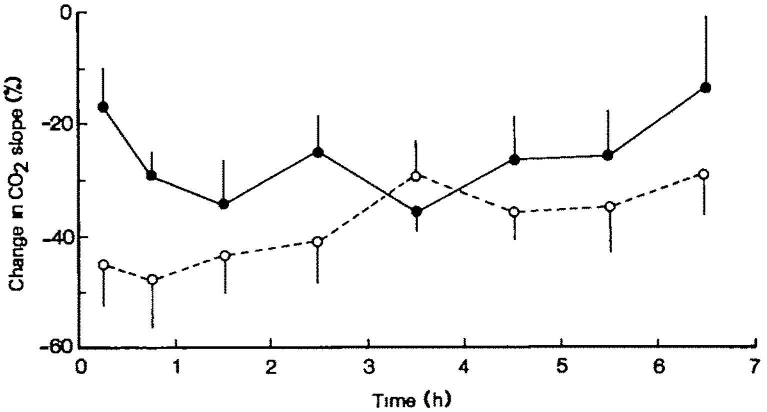

FIG. 5. Percentage change of slope of carbon dioxide response curve ($\Delta\dot{V}\text{E}/\Delta P\text{E}'_{\text{CO}_2}$) after extradural sufentanil 50 µg (means ± SEM). ○ = Plain sufentanil; ● = sufentanil + adrenaline.

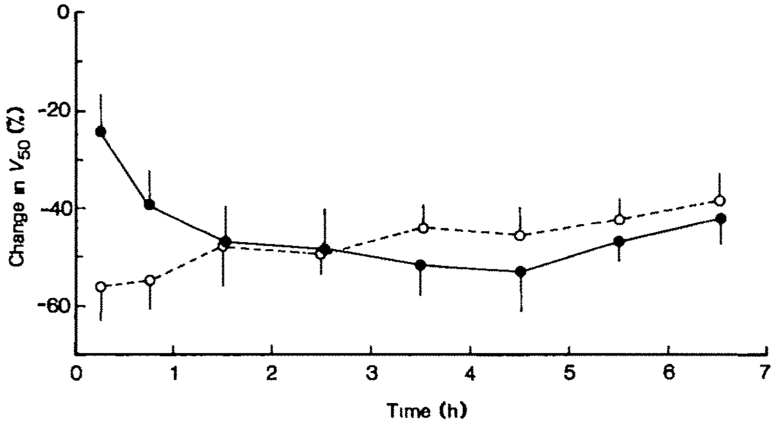

FIG. 6. Percentage change of $\dot{V}\text{E}_{50}$ after extradural sufentanil 50 µg (means ± SEM). ○ = Plain sufentanil; ● = sufentanil + adrenaline.

gradual increase to a peak of 14% above control by 4.5 h, which then declined to 8% above control by the 7th hour (fig. 4). Responses to acute carbon dioxide challenge showed a similar temporal pattern (figs 5, 6). Depression of the slope of the carbon dioxide response curve by 47.5% and of $\dot{V}_{E_{50}}$ by 56% was abrupt and marked with plain sufentanil, whereas sufentanil with adrenaline induced a more gradual depression of the slope to −36% by the 4th hour and a reduction of $\dot{V}_{E_{50}}$ to −53% in the 5th hour, followed by a gradual but incomplete recovery by the 7th hour (fig. 6). A few apnoeic periods of longer than 10 s were observed, but none exceeded 30 s.

Non-respiratory side effects

Non-respiratory side effects developed almost as rapidly as segmental analgesia and were evident within 30 min of the administration of the sufentanil, except in one subject who developed mild and probably unrelated headache for 4 h after sufentanil plus adrenaline. Incidence, intensity and duration of side effects tended to be greater with plain sufentanil than with sufentanil plus adrenaline, and this difference was most marked in the case of drowsiness (table II). This ameliorating effect of adrenaline on non-respiratory side effects was unexpected, since it was in direct contrast to our earlier studies with extradural morphine, where all side effects were made worse by adding adrenaline (Bromage et al., 1983). No arterial hypotension occurred and dizziness and light-headedness were not accompanied by any cardiovascular instability.

Risk : benefit ratio

Seven post-drug measurements of CPRT and carbon dioxide response were obtained in eight subjects at each of the two study sessions, yielding a total of 112 data points for percentage depression of CPRT and percentage depression of carbon dioxide response slope. Table III shows the distribution of these points in terms of greater or less than 50% depression of either index. The

TABLE II. *Incidence, intensity and duration of non-respiratory side-effects after extradural sufentanil 50 μg with and without adrenaline.* *P < 0.05 (*Fisher's exact test*); *NA = not applicable*

	Plain sufentanil (n = 10)			Sufentanil plus adrenaline (n = 8)		
Symptoms	Incidence	Average intensity scale (1−3)	Average duration (h)	Incidence	Average intensity scale (1–3)	Average duration (h)
Pruritus	7/10	0.9	4.0	7/8	1.2	1.7
Nausea	2/10	0.35	2.75	1/8	0.2	0.1
Dizziness	2/10	0.2	0.25	1/8	0.125	0.05
Headache	1/10	0.2	7.0	2/8	0.3	5.0
Light headedness	7/10	1.05	1.6	1/8	0.1	0.02
Drowsiness	7/10*	1.1	4.0	0*	0	0
Urinary retention	3/10	NA	5.0	1/8	NA	6.0

TABLE III. *Comparative safety and efficacy of plain sufentanil and sufentanil with adrenaline 1:200000, from 112 observations of CPRT and carbon dioxide response in eight subjects. Safety: Sufentanil with adrenaline superior to sufentanil ($\chi^2 = 5.714$, P < 0.025). Efficacy: Sufentanil with adrenaline superior to sufentanil ($\chi^2 = 4.057$, P < 0.05)*

	Safety (< 50% depression of $\Delta\dot{V}_E/\Delta P'_{E_{CO_2}}$)		Efficacy (> 50% depression of CPRT)	
	Safe	Unsafe	Effective	Ineffective
Plain sufentanil	39	17	38	18
Sufentanil + adrenaline	50	6	48	8

distribution indicates that adrenaline reduced risk significantly ($P < 0.025$) while conferring a significant improvement in efficacy ($P < 0.05$).

DISCUSSION

Laboratory investigations of analgesic efficacy and safety may be criticized as irrelevant to clinical management but, on the contrary, they provide insight to questions which could not be answered in any other way, and they fill a void left by the inadequacies in the design of postoperative investigations. Postoperative patients make poor subjects. They are fatigued and in pain, and they cannot be relied upon to co-operate effectively and consistently, for many hours on end, in physically demanding studies. One analysis of postoperative hypercapnic responses concluded that approximately one-half of all such estimates may have to be excluded as unreliable (Goodman and Black, 1985). In another study of pain and postoperative analgesia one of us (P.R.B.) found that two out of three pulmonary pressure–volume estimations were technically unacceptable, and the investigation was abandoned.

On the other hand, healthy volunteers are sturdy, articulate subjects with the stamina to provide consistent responses throughout a long and gruelling programme. While laboratory algesimetry cannot mirror surgical pain precisely, it serves as an acceptable approximation and provides a proving ground to study the effects of altering one variable at a time, and to guide appropriate designs for subsequent clinical trials.

In this study, greatest emphasis has been placed on two objective tests, the cold pressor response and measurements of central respiratory drive. The cold pressor response test simultaneously performs tasks of both generating pain and measuring the response in an objective and consistently repeatable manner that is free of acute tolerance, conscious control or decision making (Hines and Brown, 1933; Godden, Roth and Hines, 1955). Although carbon dioxide responses vary widely between individuals, and even from day to day, measurements in males on any given day are highly repeatable, with a coefficient of variation of about 15% (Sahn et al., 1977; Scamman and Ghoneim, 1983).

Two subjective tests, periosteal pressure and the linear analogue scale, were included as supportive data. The linear analogue scale plays the additional and important role of documenting a simple, unsophisticated link between this study and others, where the linear analogue was used in an attempt to quantitate laboratory or clinical pain and analgesia. Thus, our control score of 7.1 with a reduction of 73%, 1 h after the administration of plain sufentanil, compares fairly closely with the results of Donadoni and colleagues (1985), who found a reduction of 96% after a similar control score and extradural dose of sufentanil following orthopaedic surgery on the lower limb.

Our algesimetric tests showed that sufentanil in 50-μg doses produced very rapid and effective analgesia of a strongly segmental nature. Limitation of segmental spread was not perfect, since an appreciable degree of analgesia was observed in the sternum and upper limb, reflecting some degree of rostral spread to the thoraco–cervical region. However, the forehead was virtually unaffected, while the upper level of cutaneous hypalgesia to pin-prick remained steadfastly fixed in the lower thoracic segments until analgesia waned. This constancy of dermatome hypalgesia was in marked contrast to earlier findings with extradural morphine, when cutaneous hypalgesia spread slowly upwards to reach trigeminal territory by the 5th–8th hours, and when adrenaline hastened and intensified this upward spread (Bromage et al., 1982, 1983).

Both subjective and objective evidence of analgesia in figures 1, 2 and 3 show that segmental hypalgesia was more sharply defined after sufentanil with adrenaline than after plain sufentanil. The separation of quality of analgesia in hand and foot, and its exaggeration by adrenaline, is seen most clearly in the linear analogue scores in figure 1. These curves may reflect a more rapid and extensive vascular uptake and systemic effect with plain sufentanil as well as a more complete uptake in the lower spinal cord with sufentanil and adrenaline. However, blood concentrations were too low and too evanescent to support any conclusions about the influence of vascular uptake. Cord uptake is likely to be the more important of these two variables, since strong subjective analgesia in the foot persisted into the 6th hour with the adrenaline solution, and far beyond the time when circulating sufentanil had become undetectable. How can these algesimetric results be translated from laboratory-induced pain to the real intensity of clinical pain? Earlier work with extradural narcotics in patients and volunteers suggests that doses sufficient to produce a 70–75% depression of CPRT provide strong analgesia, equivalent to that required to alleviate severe postoperative pain associated with upper abdominal or thoracic surgery. A 50% depression of CPRT is roughly equivalent to the degree of analgesia required for less severe pain associated with lower abdominal procedures (Bromage, Camporesi and Chestnutt, 1980; Bromage, Camporesi and Leslie, 1980; Bromage et al., 1983).

If such an equivalent scale is applied to figures 1 and 3, it can be estimated that plain extradural sufentanil in a 50-µg dose will provide about 1.5 h of adequate analgesia for upper abdominal pain and about 3.5 h of satisfactory pain relief from lower abdominal pain. The adrenaline-containing solution will give a similar degree of relief for 4.5 h after upper abdominal surgery and for 5.5 h after lower abdominal operations. These estimates of duration of clinical analgesia may be conservative, for they fall short of the figure of 5–6 h reported by Donadoni and colleagues (1985) after 50 µg of the plain solution following lower limb surgery.

The non-respiratory effects of pruritus, nausea, retention of urine and depressed mentation were of trivial severity and incidence when compared with extradural morphine 10 mg in volunteers, and unlike morphine or fentanyl, these unwelcome side effects were diminished rather than worsened by the addition of adrenaline (Bromage et al., 1983; Welchew, 1983; Robertson, Douglas and McMorland, 1985).

Unfortunately, as in all other volunteer studies in which respiratory control has been measured, respiratory depression accompanied analgesia. However, the effects of adrenaline as an adjuvant to extradural sufentanil were markedly different from its action with extradural morphine in volunteers, in whom adrenaline caused a proportionate increase in both analgesia and undesirable side effects, including alarmingly long apnoeic intervals lasting from 15 to 50 s (Bromage et al., 1983; Camporesi et al., 1983). In the present series, adrenaline intensified and prolonged segmental analgesia without causing a corresponding increase in respiratory depression.

In summary, our results show that extradural sufentanil 50 µg provides effective analgesia of 2–3 h duration, and that intensity of analgesia is enhanced and duration prolonged to 4.5–5.5 h by the addition of adrenaline 5 µg ml^{-1}. Both non-respiratory and respiratory side effects are less when adrenaline is added to sufentanil. This favourable performance of sufentanil with adrenaline, in volunteers, suggests that the combination is suitable for wider evaluation under conditions of clinical trial.

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ANALYSIS OF SUXAMETHONIUM SENSITIVITY FOLLOWING TERMINATION OF PREGNANCY

M. WHITTAKER AND J. J. BRITTEN

SUMMARY

The cholinesterase genotypes in the majority (25/35) of patients with suxamethonium sensitivity following termination of pregnancy are heterozygotes with an E_1^a *gene. Twelve of these patients have the genotype* $E_1^uE_1^a$*. The reported duration of apnoea is minimal in the heterozygotes lacking the* E_1^a *gene (about 5–10 min) and maximal in the homozygotes* $E_1^aE_1^a$ *(about 35 min). With few exceptions, the heterozygotes having an* E_1^a *gene are apnoeic for 10–15 min. The apparent low frequency of suxamethonium in these patients is discussed.*

One of the physiological factors associated with pregnancy is a significant decrease (about 20%) in plasma cholinesterase activity (Piccoli and Longo, 1947; Robertson, 1966). Although some ambiguity has arisen about the pattern of change in the enzymic activity during pregnancy, it is now accepted that a rapid decrease in cholinesterase activity occurs during the first trimester of pregnancy (Levine and Hoyt, 1949; Evans and Wroe, 1980). The decrease in activity is sustained until delivery.

Plasma cholinesterase variants have decreased enzymic activity relative to the usual homozygote $E_1^uE_1^u$ (Whittaker, 1986). Heterozygotes in general are not sensitive to suxamethonium, but a rather longer period of muscle paralysis, of not more than 10 min (compared with about 2–4 min for the usual homozygote) is observed. Indeed, some anaesthetists can predict a heterozygote from observation of the duration of paralysis following the administration of a standard dose of suxamethonium to their patients (Vickers, personal communication). It is, therefore, desirable to ascertain the effect of pregnancy on the duration of apnoea in heterozygotes following a standard dose of suxamethonium. Blood samples from patients showing sensitivity to suxamethonium following termination of pregnancy have been sent to Exeter for phenotyping of cholinesterase variants. These samples were the basis of this study.

MATERIALS AND METHODS

Thirty-five blood samples, from patients in the same Nursing Home, were phenotyped for cholinesterase variants during a 3-year period. All patients were reported to have experienced suxamethonium sensitivity following anaesthesia for the termination of pregnancy. The operative procedure was usually of about 5 min duration. This necessitated a brief anaesthetic which consisted of a barbiturate i.v. (usually methohexitone, but sometimes thiopentone) and intermittent positive pressure ventilation using nitrous oxide and oxygen. The trachea was not intubated. A small dose of suxamethonium (usually 20–25 mg or less) was used and, in consequence, the apnoea was very transient. Recovery of spontaneous respiration almost invariably occurred before the patient was ready to be lifted off the operating table. The definition of "scoline apnoea" in these patients was inadequate ventilation 2–3 min on the trolley after being lifted off the table. Thus the minimum period for an apnoea was approximately 10 min. A 10-ml, heparinized blood sample was sent for phenotyping for all patients who experienced an apnoea of 10 min or longer. Cholinesterase activity was assayed by the method of Kalow and Lindsay (1955) and genotyped by measuring dibucaine, fluoride and RO2 numbers (Whittaker, 1986).

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TABLE I. *Mean duration of apnoea and percentage distribution of genotypes in 35 suxamethonium-sensitive individuals following termination of pregnancy*

	Genotype						
	$E_1^uE_1^s$	$E_1^uE_1^f$	$E_1^uE_1^a$	$E_1^aE_1^f$	$E_1^aE_1^k$	$E_1^aE_1^j$	$E_1^aE_1^a$
Number of patients	2	1	12	5	6	2	7
Percentage distribution	5.7	2.9	34.3	14.3	17.1	5.7	20.0
Duration of apnoea (min)							
Mean	7.5	4.0	15.0	8.4	8.8	15.0	35.6
Range	5–10	4	5–25	7–10	5–12	10–20	15–69

RESULTS

The distribution of genotypes found in 35 suxamethonium-sensitive patients is given in table I. The range and mean duration of apnoea for each genotype are also included in the table.

DISCUSSION

It is apparent from the results given in table I that the individuals who experienced sensitivity to suxamethonium following the termination of pregnancy were not confined to the cholinesterase genotypes $E_1^aE_1^a$ and $E_1^aE_1^s$. In this study nearly 70% of the patients were heterozygotes having an E_1^a gene. This closely matches our earlier observation that an increased frequency of suxamethonium sensitivity occurs in the heterozygotes $E_1^uE_1^a$ during pregnancy (Whittaker, 1980). At that time we did not differentiate between the heterozygotes $E_1^uE_1^a$, $E_1^aE_1^k$ or $E_1^aE_1^j$. A frequency of about 7% has been reported for the $E_1^uE_1^a$ heterozygote in suxamethonium-sensitive surveys of ECT patients (Owen and Hunter, 1983) and general surgical patients (Lehmann and Liddell, 1969; Viby-Mogensen and Hanel, 1978).

Analysis of the results of the present study has not differentiated between the genotypes $E_1^aE_1^a$ and $E_1^aE_1^s$—both types have been classified as $E_1^aE_1^a$. In this survey only nine patients (one $E_1^aE_1^a$ phenotype) have accepted family studies. Thus it is impossible, in the absence of family confirmation, to assign a silent gene as a true interpretation of a low enzymic activity when the condition of pregnancy produces such an effect. However, very few previous surveys of the distribution of phenotypes occurring in suxamethonium-sensitive individuals have segregated these two genotypes and 43.2% of 1346 sensitive individuals have the $E_1^aE_1^a$ phenotype (Whittaker, 1986). It is universally accepted that all individuals having this phenotype are sensitive to suxamethonium but, in the current study, we have found only 20% with this phenotype. The discrepancy may be explained by the size of sample or, more probably, by the large increase in frequencies of the heterozygotes $E_1^uE_1^a$ and $E_1^aE_1^k$ (50% compared with 10.5% from the 1346 individuals reported above).

An ancillary approach to the validity of the 20% atypical homozygotes in our survey can be assessed by comparing the theoretical and actual number of patients being anaesthetized in this hospital each year during the 3-year period of the study. The frequency of the $E_1^aE_1^a$ phenotype in a British population is approximately 1 in 1800. This frequency can be used to estimate the number of females presented for surgery in this Nursing Home during the 3 years of the survey as 7 × 1800 = 12600 or about 4200 per annum. The Records Department has supplied figures of 7967, 8401 and 8578 for the 3 years covered by the survey. An annual average of 8315 patients is at variance with our estimate. This apparently low incidence of suxamethonium sensitivity in our study could be partially explained by the use of other neuromuscular blocking drugs in some patients undergoing sterilization or, rarely, other surgery. All our patients showed suxamethonium sensitivity during the termination of their pregnancies. It is also possible that a proportion of patients who did show sensitivity to suxamethonium were not referred, for various reasons, for phenotyping of the cholinesterase variants.

Viby-Mogensen (1982) has studied the reaction of phenotypically different cholinesterase to suxamethonium using train-of-four nerve stimulation. He demonstrated that the existence of two abnormal genes, compared with only one, dramatically changes the response to the drug in so far as the duration of apnoea, and the time for recovery of adequate ventilation, are significantly prolonged. Our records for the present survey confirm these observations for the $E_1^aE_1^a$ phenotype, but no substantial prolongation of apnoea is apparent in either the $E_1^aE_1^f$ or the $E_1^aE_1^k$ genotypes. Our sample is small with only five and six of these heterozygotes, respectively.

Evidence for the ambiguity of sensitivity of the $E_1^uE_1^a$ heterozygote also has been provided by Viby-Mogensen (1981). He showed that 50% of these heterozygotes experience a moderately prolonged response to suxamethonium and 10% of these individuals did not have normal neuromuscular transmission, as demonstrated by train-of-four nerve stimulation, for 20 min. At that time Viby-Mogensen (1981) did not differentiate between the heterozygotes $E_1^uE_1^a$ and $E_1^aE_1^k$, but in the current study only the heterozygotes $E_1^uE_1^a$ are reported to have an apnoea of 20–25 min. Our results support the observation of Viby-Mogensen (1981) that heterozygote patients will develop an apnoea more readily than the usual homozygote, $E_1^uE_1^u$.

We have found no correlation between the duration of apnoea and cholinesterase activity, but it is apparent from the results in table I that the duration of apnoea is very dependent on the genotype of the pregnant patient.

The vast majority of reports of suxamethonium-sensitive individuals have not used a nerve stimulator to demonstrate prolonged neuromuscular blockade and thus confirm the drug-induced apnoea. Some patients are over ventilated and apnoea as a result of hypocapnia can be misinterpreted as suxamethonium sensitivity. From a surgical population of 24945 pregnant patients seeking termination of pregnancy, 35 individuals have been found to be sensitive to suxamethonium. This low frequency of sensitivity provides scant evidence for the avoidance of the use of suxamethonium in women seeking termination of pregnancy.

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ADDITIONAL BLOOD-GAS VARIABLES FOR THE RATIONAL CONTROL OF OXYGEN THERAPY†

With Allowance for Shifts of the Oxygen Dissociation Curve

N. WILLIS, M. C. C. CLAPHAM AND W. W. MAPLESON

SUMMARY

When a sample of arterial blood is analysed for oxygen tension and, using a modern oximeter, for haemoglobin concentration and saturation, it is possible to calculate the position of the oxygen dissociation curve and two new variables: "P_{95}" and "$C(a-x)_{O_2}$". P_{95} is the tension at which the haemoglobin would be 95% saturated and can, therefore, constitute a target tension for near-maximum arterial content of oxygen. $C(a-x)_{O_2}$ (the "conditional extraction" of oxygen) is the amount of oxygen, in ml/dl blood, which can be extracted from the arterial blood for a hypothetical mixed-venous oxygen tension Px_{O_2}. It is explained how it is possible to estimate the adequacy of tissue oxygenation by comparing any available estimate of the required extraction (normally about 5 ml dl^{-1}) with conditional extractions calculated for three hypothetical values of Px_{O_2} covering the clinical range. Methods of calculation are given. For accurate results at high arterial saturations, a peripheral venous sample may be required in addition to the arterial sample.

Since the introduction of the polarographic electrode by Clark (1956), measurements of the oxygen tension of blood have been readily available. With modern oximeters, accurate measurements of the oxygen saturation and haemoglobin concentration of blood samples are also possible. Furthermore, with cheap, powerful computers it is now possible to use these data to calculate additional variables to assist in the management of oxygen therapy. This paper examines some of the factors involved and suggests additional variables for routine reporting.

THEORETICAL CONSIDERATIONS

Figure 1 shows a normal oxygen dissociation curve. On the plateau of the curve, above say 10 kPa (75 mm Hg), saturation is near maximum and little altered by changes of tension. Therefore, if a sample of arterial blood has an oxygen tension (Pa_{O_2}) which is on the plateau, the excess of the Pa_{O_2} over about 8–10 kPa (60–75 mm Hg) provides a measure of how much tension is "in hand" before deterioration of respiratory function brings the patient to the edge of the plateau. At this point, further decrease of tension leads to rapidly decreasing saturation (Sa_{O_2}) and, hence, rapidly decreasing delivery of oxygen to the tissues. This is consistent with current advice (Downs, 1982; Sampliner and Pitluk, 1982; Shoemaker, Appel and Bland, 1983) to aim for a Pa_{O_2} greater than 70 mm Hg (9.3 kPa).

However, the oxygen dissociation curve is often displaced from its normal position in patients undergoing respiratory therapy. In samples coming to our blood-gas laboratory from adults, displacements commonly range from 10% shifted to the left to 30% shifted to the right. Figure 2 shows curves with these shifts (thin lines) as well as the normal curve (thick line). It can be seen

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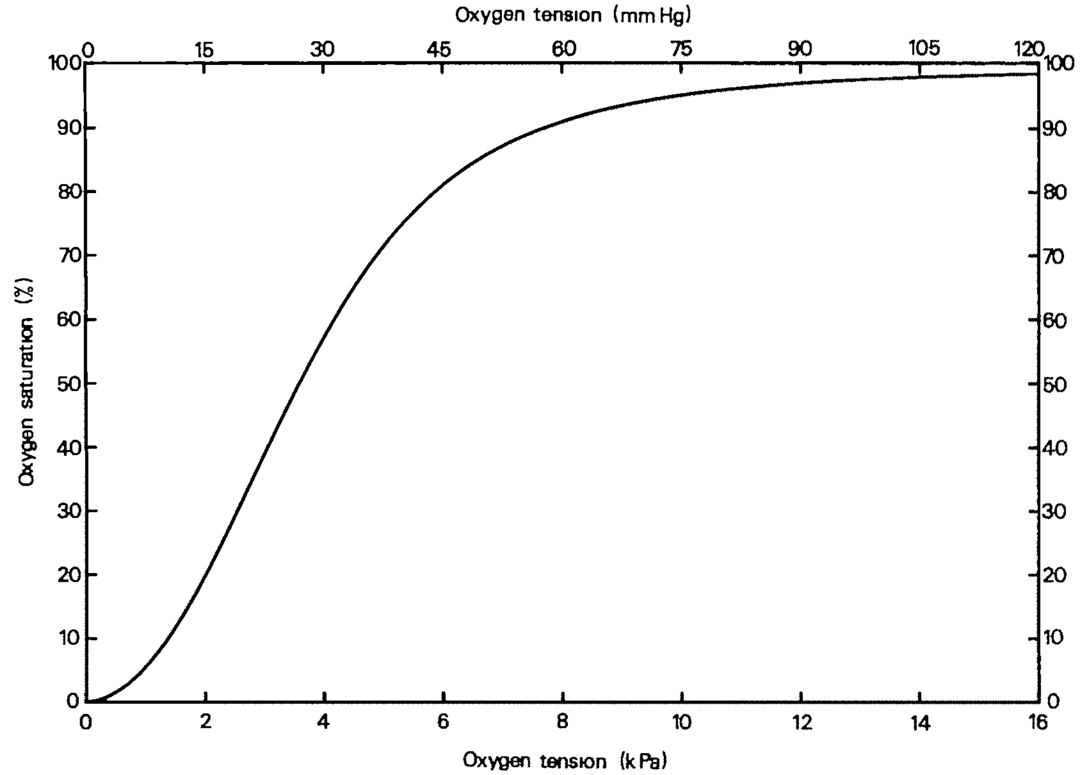

FIG. 1. The normal oxygen dissociation curve (Appendix 1, equation (1)).

that to achieve 95% saturation may require a Pa_{O_2} of anything from 9 to 13 kPa (roughly 70–100 mm Hg). Therefore, it would be of value to know the position of the dissociation curve in the individual patient.

Determining the position of the curve used to be a difficult and tedious procedure. Now, modern oximeters can measure saturation as simply, and about as accurately, as blood-gas analysers measure tension. If both tension and saturation are measured in a single sample of blood, one point on the particular dissociation curve will be determined. Then, since the general equation to the curve is well known (devised by Adair (1925) and quantified by Kelman (1966) and Thomas (1972)), the particular dissociation curve can be characterized fully.

The position of a dissociation curve is often quoted in terms of its "P_{50}"—the Po_2 at which the haemoglobin is 50% saturated. The P_{50} is an important theoretical parameter of an early (Hill, 1910) equation to the dissociation curve, but it is not of much direct clinical significance. Therefore, it is proposed that the blood-gas laboratory should report the position of the curve in terms of its percentage shift from normal. It is also proposed that the laboratory should report the "P_{95}", the Po_2 at which the haemoglobin will be 95% saturated. Then the clinician can aim for a slightly greater Pa_{O_2}, knowing that near-maximum saturation will just be achieved, whatever the position of the curve.

However, 95%, or any other high, fixed saturation, is not necessarily the best target. For instance, if the haemoglobin concentration is low, then even near-maximum saturation may result in inadequate availability of oxygen to the tissues. On the other hand, if a high saturation can be achieved only at the cost of intense oxygen therapy, the high inspired concentration of oxygen may damage the lungs and a high level of positive end-expiratory pressure (PEEP) may decrease cardiac output. Therefore, it is relevant to question whether, in the particular patient, maximum saturation is necessary and, if necessary, whether it is sufficient.

Measurement of individual tissue oxygen tension would provide an ideal guide to the adequacy

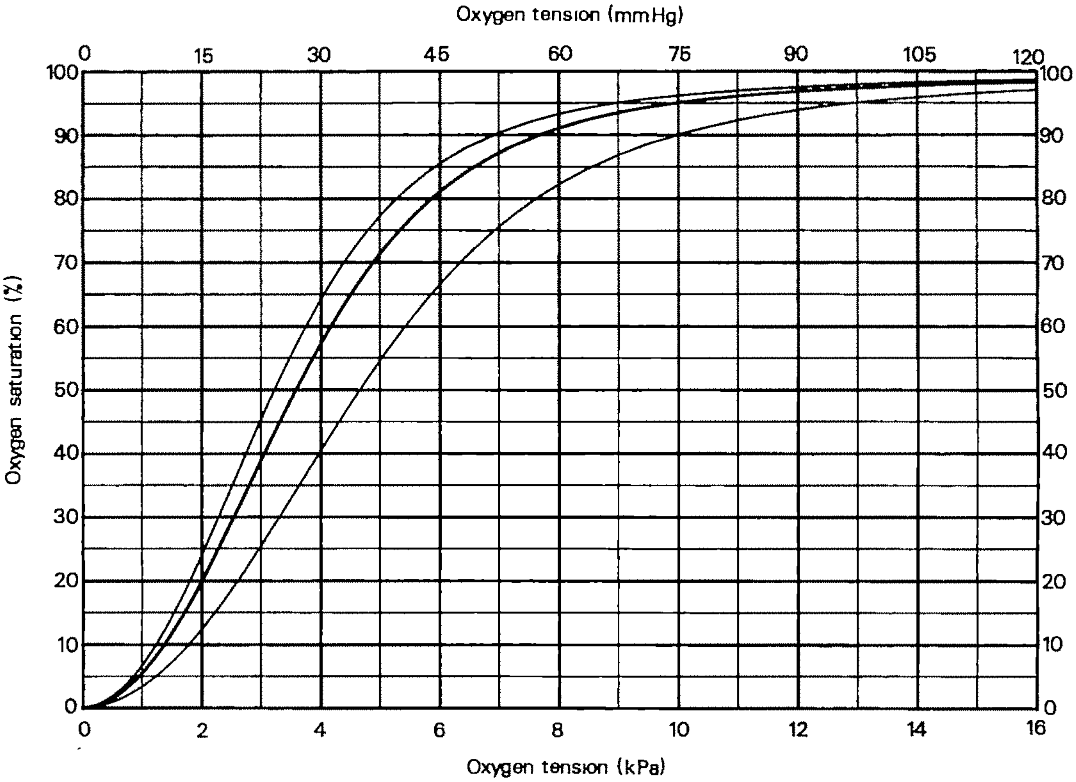

FIG. 2. Three oxygen dissociation curves: 10% left-shifted, that is with a P_{O_2} 10% less than in the normal curve (for any given S_{O_2}); normal; and 30% right-shifted (P_{O_2} 30% greater than in the normal curve). (Appendix 1, equations (1) and (3).)

of oxygen delivery, but that is hardly practical. Mixed-venous oxygen tension ($P\bar{v}_{O_2}$) represents a good substitute guide to overall adequacy, but the invasiveness of its measurement is not always justified. Therefore, the assessment of the adequacy of tissue oxygenation must be approached indirectly. We believe that the new facilities can form the basis of such an approach.

The oxygen requirements of the tissues can be considered either in terms of the required oxygen consumption (in ml min^{-1}), or in terms of the required extraction of oxygen from arterial blood (in ml/dl blood). The two are related by the cardiac output (fig. 3). Here the arguments are presented first in terms of oxygen extraction.

Modern oximeters measure the total haemoglobin concentration (Hb) as well as its saturation. If Pa_{O_2}, Sa_{O_2}, and Hb are all measured, it is possible to calculate (Appendix 1) the oxygen content of arterial blood (Ca_{O_2}) as well as the position of the dissociation curve. If, then, some hypothetical $P\bar{v}_{O_2}$, "Px_{O_2}", is postulated, it is possible to calculate the corresponding saturation (Sx_{O_2}) and content (Cx_{O_2}). Hence, by difference, it is possible to obtain the content difference between that measured in arterial blood and the content of mixed-venous blood at the hypothetical tension Px_{O_2}. This is here called "$C(a-x)_{O_2}$" and can usefully be referred to as the "conditional extraction" of oxygen (the amount of oxygen in ml/dl blood, which, if it were extracted, would lead to a mixed-venous tension equal to Px_{O_2}).

It is proposed to calculate and report this $C(a-x)_{O_2}$ for three values of Px_{O_2}: 5.3 kPa (40 mm Hg) (normal); 2.7 kPa (20 mm Hg) (about the lowest possible value, below which the tissues can extract no more oxygen (Bryan-Brown et al., 1973)); and 4.0 kPa (30 mm Hg) (half way between the two and a little above the 3.7 kPa at which blood lactate concentration is increased (Kasnitz et al., 1976)).

In order to interpret these "conditional extractions" (these values of $C(a-x)_{O_2}$) it is necessary to know what extraction is *required* for

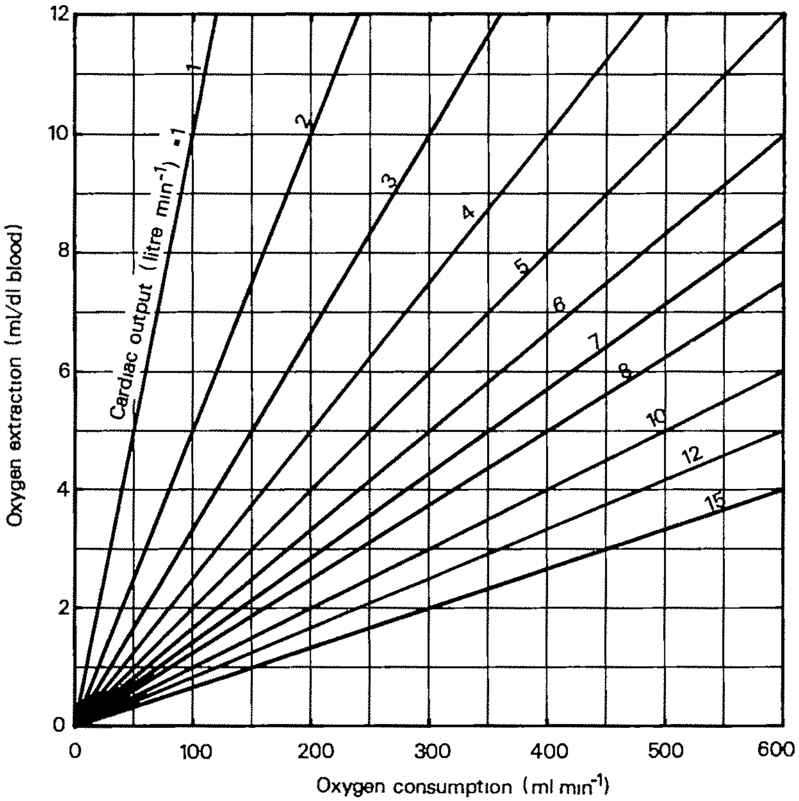

FIG. 3. The relation between oxygen extraction, oxygen consumption and cardiac output. If the x-axis is entered at the actual, required or conditional oxygen consumption, the y-axis indicates respectively, for any given cardiac output, the corresponding actual, required or conditional oxygen extraction.

adequate oxygenation of the tissues. In general this is given by:

Required oxygen extraction =

$$\frac{\text{required oxygen consumption (ml min}^{-1}\text{)}}{\text{cardiac output (litre min}^{-1}\text{)}}$$

Usually, the cardiac output is not measured and, even if the actual oxygen consumption is measured, this may be limited to less than the required consumption by the condition of the patient, resulting in increased lactate production. However, in a normal person at rest, the consumption is about 250 ml min^{-1} and the cardiac output about 5 litre min^{-1}, giving a required extraction of 50 ml litre^{-1} or 5 ml dl^{-1}. For a particular patient, this normal requirement will be increased in conditions of hyperthermia or low cardiac output and can be adjusted upwards or, for the reverse circumstances, downwards. If the clinician is prepared to make numerical estimates of the cardiac output and the required consumption, then the required extraction can be read from figure 3. Whatever estimate of required extraction is in fact adopted can then be compared with the three values of $C(a-x)_{O_2}$ for the three hypothetical $P\bar{v}_{O_2}$ and a probable actual $P\bar{v}_{O_2}$ estimated by interpolation. (The method is made clearer by some examples below.) The clinician can then adjust treatment accordingly: intensifying or relaxing the oxygen therapy, increasing the haemoglobin concentration, or trying to shift the dissociation curve to a more favourable position (see below).

An alternative way to use the $C(a-x)_{O_2}$ is to decide on the lowest $P\bar{v}_{O_2}$ to which it is thought reasonable to expose the patient and then, by interpolation between the three values of $C(a-x)_{O_2}$, estimate the corresponding conditional extraction and consider whether it is adequate.

If the clinician prefers to think in terms of oxygen consumption rather than oxygen extraction, it is necessary to have some quantitative

TABLE I. *Hypothetical examples of data to be offered to the clinician from a sample of arterial blood of haemoglobin concentration 10 g* dl^{-1}. †*Shift of the oxygen dissociation curve for arterial blood (negative values = left shift).* ††*"Available" haemoglobin (excluding COHb and MetHb).* ‡*Calculated assuming that venous blood is 4.4% right shifted with respect to arterial blood*

	Measured variables				Calculated variables					
								$C(a\text{-}x)_{O_2}$ (ml dl^{-1}) ("conditional extraction")‡		
Line no.	Pa_{O_2} (kPa)	Sa_{O_2} (%)	Hb†† (g dl^{-1})	ODC shift† (%)	P_{50} (kPa)	P_{90} (kPa)	P_{95} (kPa)	Px_{O_2} = 2.7	Px_{O_2} = 4.0	Px_{O_2} = 5.3
1	6.0	85.5	10.0	−10.0	3.2	6.9	8.9	6.9	3.5	1.1
2	6.0	81.0	10.0	0.0	3.6	7.7	9.9	7.1	3.8	1.2
3	6.0	66.5	10.0	30.0	4.7	10.0	12.9	6.5	3.9	1.4
4	8.0	93.3	10.0	−10.0	3.2	6.9	8.9	8.1	4.6	2.2
5	8.0	91.0	10.0	0.0	3.6	7.7	9.9	8.5	5.2	2.7
6	8.0	82.2	10.0	30.0	4.7	10.0	12.9	8.7	6.2	3.7
7	10.0	96.2	10.0	−10.0	3.2	6.9	8.9	8.5	5.1	2.7
8	10.0	95.1	10.0	0.0	3.6	7.7	9.9	9.1	5.8	3.3
9	10.0	90.0	10.0	30.0	4.7	10.0	12.9	9.9	7.3	4.8
10	12.0	97.6	10.0	−10.0	3.2	6.9	8.9	8.8	5.3	2.9
11	12.0	96.9	10.0	0.0	3.6	7.7	9.9	9.4	6.1	3.6
12	12.0	93.9	10.0	30.0	4.7	10.0	12.9	10.4	7.9	5.4
13	14.0	98.3	10.0	−10.0	3.2	6.9	8.9	8.9	5.4	3.1
14	14.0	97.8	10.0	0.0	3.6	7.7	9.9	9.6	6.3	3.8
15	14.0	95.9	10.0	30.0	4.7	10.0	12.9	10.8	8.2	5.7

estimate, however approximate, of cardiac output. Then the three reported conditional extractions can be converted to conditional oxygen consumptions by calculation, or with the aid of figure 3. If a required oxygen consumption has been decided upon, this can be interpolated between the three conditional consumptions to provide an estimate of the mixed-venous oxygen tension. Alternatively, a minimum acceptable mixed-venous tension can be decided upon and the corresponding interpolated conditional oxygen consumption assessed for adequacy.

EXAMPLES

Table I lists examples of the proposed additional variables, calculated for five different values of Pa_{O_2} and three different oxygen dissociation curves (10% left shifted, normal, and 30% right shifted—as illustrated in figure 2), all for a haemoglobin concentration of 10 g dl^{-1}. This concentration has been chosen so that values of $C(a-x)_{O_2}$ for other haemoglobin concentrations can be obtained simply by multiplying by Hb/10 (apart from a slight error arising from the dissolved oxygen not changing with Hb). In addition, 10 g dl^{-1} is near the middle of the range for samples coming to our blood-gas laboratory. Values of P_{90} (the Po_2 at which haemoglobin is 90% saturated) as well as of P_{95}, are included. So also are values of P_{50} for the benefit of those who think of the shift of the dissociation curve in those terms. Thus each line contains the information which might be presented to the clinician as the results from a single arterial sample. A few lines will be considered in some detail to illustrate how the information might be interpreted. The reader may find it helpful to follow the examples on the graph of figure 2.

Line 8 represents a patient with a normal dissociation curve and a Pa_{O_2} of 10 kPa (75 mm Hg). This gives an arterial saturation of 95.1% but, because of the low Hb, a normal $P\bar{v}_{O_2}$ of 5.3 kPa (40 mm Hg) will give a conditional (extraction ($C(a-x)_{O_2}$) of only 3.3 ml dl^{-1}. However, the conditional extraction for a $P\bar{v}_{O_2}$ of 4.0 kPa (30 mm Hg) ($C(a-4.0)_{O_2}$) is 5.8 ml dl^{-1}. Therefore, unless the required extraction is above the normal 5 ml dl^{-1}, there is unlikely to be any increase in blood lactate concentration.

Line 9 represents a patient with the same Pa_{O_2} (10 kPa) but with a dissociation curve which is 30% right shifted. In this case the Pa_{O_2} is well below the P_{95} (now 12.9 kPa), giving an arterial saturation of only 90% and inviting and intensification of the oxygen therapy. However, the conditional extractions are now considerably better: a normal extraction of 5 ml dl^{-1} can be achieved with a $P\bar{v}_{O_2}$ only a little less than the normal 5.3 kPa ($C(a-5.3)_{O_2} = 4.8$ ml dl^{-1}). Therefore, even if the required oxygen extraction is somewhat increased, there is unlikely to be any increase in lactate concentration. Accordingly, it is probably not necessary to intensify the oxygen therapy and, if that therapy is already intense, there may even be a case for relaxing it a little.

Line 7 represents a patient with an oxygen dissociation curve which is 10% left shifted but again with a Pa_{O_2} of 10 kPa. This is now appreciably greater than the P_{95} of 8.9 kPa and is associated with 96.2% saturation. However, despite this near-maximum saturation, and because of the low haemoglobin concentration and the left shift, a normal extraction of 5 ml dl^{-1} will result in a $P\bar{v}_{O_2}$ of about 4 kPa ($C(a-4.0)_{O_2} = 5.1$ ml dl^{-1}). If this is taken as an indication for improving the availability of oxygen to the tissues, there is little point in intensifying the oxygen therapy because the arterial saturation is already very high. If it is decided to increase the haemoglobin concentration it should be remembered that infusions of blood or packed cells usually result in a left shift (unless the blood is very fresh or has been specially pre-treated) and inspection of table I shows that this nearly always decreases the conditional extraction. Therefore, treatment might best be directed towards shifting the dissociation curve to the right, with or without increasing the haemoglobin concentration. Alternatively, the results might simply be taken as a justification for inserting a pulmonary artery catheter in order to find the true value of the mixed-venous tension.

Line 13 might represent the same patient subjected to enthusiastic oxygen therapy: with the same 10% left shift, the Pa_{O_2} stands at 14 kPa (105 mm Hg)—very much more than the P_{95}. This invites relaxation of the oxygen therapy. If this is done sufficiently to decrease the Pa_{O_2} to 10 kPa it would reduce the extraction for a $P\bar{v}_{O_2}$ of 4.0 kPa only from 5.4 to 5.1 ml dl^{-1} (compare lines 13 and 7). Furthermore, if the relaxation of the therapy included a reduction in PEEP, this might lead to an increase in cardiac output and, hence, to a decrease in the required extraction. On balance, there might even be a small improvement in tissue oxygenation. However, if 4 kPa is considered too low for the $P\bar{v}_{O_2}$, or if the required extraction is thought to be greater than 5 ml dl^{-1}, then the arguments adduced above in relation to line 7 of the table are relevant.

At the other extreme, lines 1–3 show that, with a very low Pa_{O_2} (6 kPa, 45 mm Hg) and a haemoglobin concentration of 10 g dl^{-1}, a normal extraction of 5 ml dl^{-1} would be achieved only with a $P\bar{v}_{O_2}$ of less than 4 kPa and, therefore, probably with increased blood lactate concentrations. Even increasing the haemoglobin concentration to a normal 14 g dl^{-1} would only just provide 5 ml dl^{-1} extraction for a $P\bar{v}_{O_2}$ of 4 kPa. It should also be noted that, at this low Pa_{O_2}, the conditional extraction is much less affected by shift and, at a postulated $P\bar{v}_{O_2}$ of 2.7 kPa (20 mm Hg), the $C(a-2.7)_{O_2}$ is actually *less* with a 30% right shifted curve (line 3) than with a normal curve (line 2). This is an example of the phenomenon noted by Turek, Kreuzer and Hoofd (1973), and by Sold (1982), that right shift (or, in their terms, decreased affinity of haemoglobin for oxygen) does not always improve the availability of oxygen to the tissues.

The reason can be deduced from figure 2. If the arterial tension is high, the saturation, and hence the content, of arterial blood is little altered by the shift of the curve (the curves are all close together vertically); on the other hand, at a normal mixed-venous tension of 5.3 kPa the curves are widely separated vertically, so that haemoglobin on the 30% right-shifted curve is about 15% less saturated than haemoglobin on the normal curve. Therefore, more oxygen is released from the right-shifted curve. Conversely, if the arterial tension is only 6 kPa (vertical separation of curves nearly maximum) and the mixed-venous tension say 3 kPa (curves beginning to come together again as they all approach zero saturation) it can be seen that the decrease in saturation from arterial to venous tension is slightly less for the right shifted curve (from 66% to 25% = 41%, compared with 81% to 38% = 43% for the normal curve). Therefore less oxygen is released from the right-shifted curve. However, in the great majority of circumstances more oxygen can be extracted by the tissues with a right-shifted curve than with a left-shifted one.

PRACTICAL CONSIDERATIONS

Modern oximeters measure not only oxyhaemoglobin (Hbo_2) and reduced haemoglobin (HHb) but also carboxyhaemoglobin (COHb) and

TABLE II. *Illustration for a hypothetical case (line 9 of table I) of a suggested layout of a report form*

MEASURED VALUES (for patient temp. = 37 °C)		
Po_2	10.0 kPa	
Saturation		
(as % of available Hb)	90.0%	
Haemoglobin	g/dl	% of total
Available	10.0	98.0
COHb	0.2	2.0
MetHb	0.0	0.0
Total	10.2	100.0
CALCULATED VALUES (for patient temp. = 37°C)		
(applicable to ARTERIAL blood only)		
P_{50}	4.7 kPa	
P_{90}	10.0 kPa	
P_{95}	12.9 kPa	
$C(a\text{-}2.7)_{O_2}$	9.9 ml/dl	
$C(a\text{-}4.0)_{O_2}$	7.3 ml/dl	
$C(a\text{-}5.3)_{O_2}$	4.8 ml/dl	
Dissociation curve is 30% RIGHT shifted.		

methaemoglobin (MetHb). The equation for the oxygen dissociation curve ((1) in Appendix 1) is based on data assembled by Severinghaus (1966) which clearly assumed that "% saturation" was calculated from Hbo_2 as a percentage of only Hbo_2+HHb and not as a percentage of total Hb. Therefore, this method of expressing % saturation must be used by the blood-gas laboratory in making its calculations (Appendix 1) and in reporting its findings. However, the information on MetHb and COHb will also be of value, although MetHb is usually negligible except as a side effect of the administration of prilocaine (Ritchie and Cohen, 1975), and in poisoning with some agricultural chemicals (Harris et al., 1979). It is also very important to distinguish measured and calculated results, and accordingly the format illustrated in table II is suggested.

The three dissociation curves drawn in figure 2 match the three used in table I but, to help interpret results obtained in clinical practice, a comprehensive set of dissociation curves, with shifts from 30% left shift to 40% right shift, at intervals of 5% are presented in figure 4. The 30% left shift is included to allow for fetal haemoglobin and for haemoglobin in stored blood (Sold, 1982). Given a result presented in the form of table II, it is possible to locate the sample as a point on figure 4. Then the figure can be used to explore the likely consequences of changing the Pa_{O_2} (moving along the curve on which the sample is located) or of treating the patient in such a way as to shift the dissociation curve. Note that the right-hand axis is scaled in approximate oxygen content. As in table I, a haemoglobin concentration of 10 g dl^{-1} has been assumed to facilitate scaling to other haemoglobin concentrations.

If the dissociation curve is to be deliberately shifted it should be remembered, as noted above, that right shifting ceases to be beneficial at very low tensions.

LIMITATIONS

The calculation of % shift, and hence of P_{95} and conditional extraction, becomes inaccurate at high saturations (Appendix 2). In these circumstances it would be necessary either for the blood-gas laboratory to equilibrate an aliquot of the arterial sample with a low Po_2 (which is time consuming) or for the clinician to supply a venous sample as well as an arterial one. A peripheral venous sample would be adequate, since the dissociation curve therein would differ from that in arterial blood only as a result of the difference in Pco_2 and pH, both of which would be measured and allowed for, according to equation (6) in Appendix 2, when calculating the shift.

The method of calculating $C(a-x)_{O_2}$, given in Appendix 1, assumes a 4.4% right shift of mixed-venous blood compared with arterial blood, based on the normal arterio-venous differences of Pco_2 and pH. Therefore, even if these differences are doubled, the resulting error in shift will be less than 5% and the resulting error in the calculated $C(a-x)_{O_2}$ will be less than 10% (Appendix 2).

The calculations assume the validity of the Thomas equation to the oxygen dissociation curve. It is known that this is invalid in the presence of substantial amounts of COHb (Zwart et al., 1984) and, therefore, the calculated values should not be reported in these circumstances. Haemoglobinopathies, also, may invalidate the Thomas equation (Bellingham, 1976), but these are rare and would generally be manifested by clinical, biochemical or haematological changes which should be taken as warnings not to report the calculated values.

If the technique is used to predict $P\bar{v}_{O_2}$ from some clinical estimate of required extraction of oxygen, it should be remembered that, if the cardiac output is maldistributed between the tissues, even a normal *mixed*-venous oxygen tension may conceal locally inadequate tissue oxygenation.

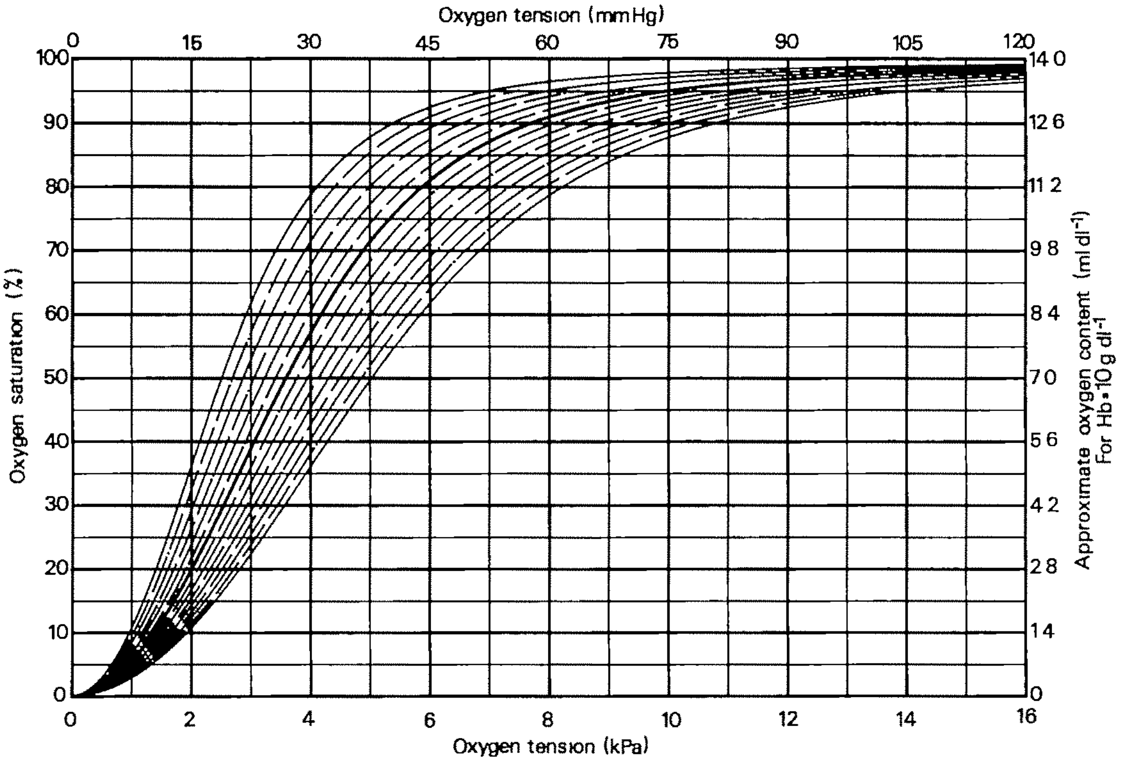

FIG. 4. Oxygen dissociation curves with shifts ranging from 30% left shift to 40% right shift in 5% steps. The normal curve is emphasized. Curves for odd multiples of 5% shift are shown by broken lines; these are omitted above 95% saturation to reduce confusion. The calibration of the right-hand y-axis is in terms of oxygen content for *10* g dl^{-1} concentration of available haemoglobin; it is approximate because the small contribution from dissolved oxygen is not proportional to saturation.

CONCLUSIONS

We think that the additional variables which we have proposed will be of value in patient care, provided that the blood-gas laboratory exercises suitable caution over accuracy of measurement of saturation (Appendix 2) and, as always, provided that the clinician supplies a valid sample. This means one which is uncontaminated by gas bubbles—or by flushing fluid when the sample has been drawn through a catheter (Clapham, Willis and Mapleson, 1987). It is also very important for the clinician to report the patient's body temperature because the location of the curve changes at the rate of 5.7% right shift per °C increase—Kelman's (1966) equation (2).

We recognize that some clinicians may prefer adaptations of these variables, or even other variables, that could be calculated from the basic measurements. It would be technically possible for each clinician to be given a personal set of variables, but this might lead to misinterpretation of results presented in unfamiliar form. Therefore, some degree of standardization is probably necessary. We hope that this paper will stimulate discussion of what standards should be adopted.

Finally, it is important to stress that the values of these calculated variables can never, in themselves, be an indication for any particular course of action. They can only be interpreted by comparison with what the clinician considers to be appropriate critical values for the particular patient. It is hoped that the new variables will help the clinician to provide better treatment.

APPENDIX 1

METHODS OF CALCULATION

The normal oxygen dissociation curve can be expressed in terms of saturation (So_2), as a function of the oxygen tension (p). Adair's (1925) equation (in a form which is efficient for computation, and which gives saturation as a percentage) is:

$$So_2 = \frac{100*p*(c_1+p*(c_2+p*(c_3+p)))}{(c_4+p*(c_5+p*(c_6+p*(c_7+p))))} \qquad (1)$$

The coefficients c_1 to c_7 have been determined empirically by Kelman (1966) and by Thomas (1972). In the present study, Thomas' values are used because they give a marginally better fit to the Severinghaus (1966) "standard" curve than those of Kelman. For p in mm Hg, $c_1 = -2000$, $c_2 = 2045$, $c_3 = 15$, $c_4 = 2400000$, $c_5 = 31100$, $c_6 = 2400$, $c_7 = 15$.

In order to obtain the tension for a known saturation the inverse function

$$p = f(So_2) \qquad (2)$$

is required. This cannot be written out as an equation; it is necessary to use an iterative, computing technique such as that outlined in figure 5.

```
min = minimum possible value of $p$ (= 0)
max = maximum possible value of $p$ (= say 1000 mm Hg)
tol = acceptable error in estimate of $p$

REPEAT
   trial_p = (min + max)/2
   trial_s = f(trial_p)
   IF trial_s > s THEN max = trial_p ELSE min = trial_p
   UNTIL (max - min) < tol
p = (min + max)/2
```

FIG. 5. An iterative routine, written in a pseudo computer language, to estimate Po_2 (p) from So_2 (s) given $s = f(p)$ (Appendix 1, equation (1)).

A z% left- or right-shifted curve is one in which, compared with the normal curve, the value of Po_2 at any given So_2 is decreased (left shift) or increased (right shift) by z%. (Technically, "sheared" would be a more appropriate term than "shifted".) Therefore

$$\frac{Po_2}{p} = 1 + z/100 \qquad (3)$$

where Po_2 is the actual Po_2 and p is what Kelman (1966) called the "virtual" Po_2—the Po_2 on the normal curve which would lead to the same saturation. For instance, in figure 2, at a saturation of 95%, the 30% right-shifted curve has an (actual) Po_2 of 13 kPa, which is 30% greater than the (virtual) Po_2 of 10 kPa associated with 95% saturation on the normal curve.

In order to determine the position of the dissociation curve in a given patient, the virtual Po_2 (p) corresponding to the measured saturation is obtained by substituting this saturation in (2). Then p, together with the measured tension (Po_2), is substituted in a rearranged version of (3):

$$z = \left(\frac{Po_2}{p} - 1\right) * 100 \qquad (4)$$

to obtain the percentage shift z. The P_{95} (or P_{90}) can then be obtained from (3), using a value for p obtained by solving (2) for a saturation of 95% (or 90%).

For any given haemoglobin concentration (Hb, in g dl^{-1}), saturation (So_2, in %), and measured tension (Po_2), the oxygen content of the blood (C, in ml dl^{-1}) is given by:

$$C = (So_2/100) * \text{Hb} * h + \alpha * Po_2 \qquad (5)$$

where h is the Hüfner factor, taken here as oxygen 1.39 ml (g Hb)$^{-1}$ (derived from the recommendations of the International Committee for Standardization in Haemotology, 1965), and α is the solubility coefficient of oxygen in blood, 0.0031 ml dl^{-1} (mm Hg)$^{-1}$ (Roughton and Severinghaus, 1973) or 0.023 ml dl^{-1} kPa^{-1}.

Therefore, in calculating $C(\text{a}-x)_{O_2}$ (from $Ca_{O_2} - Cx_{O_2}$) Ca_{O_2} is obtained by substituting the measured Sa_{O_2} and measured Pa_{O_2} in (5). However, in calculating Cx_{O_2} (the content of mixed-venous blood if the mixed-venous tension is Px_{O_2}), it is necessary to allow for the fact that mixed-venous blood is normally 4.4% right shifted with respect to arterial blood (based on an arterio–venous difference of pH of 0.04, an arterio:venous ratio of Pco_2 of 0.87, and equation (6) below). Therefore, for each postulated actual Px_{O_2} (2.7, 4.0 or 5.3 kPa), a virtual Px_{O_2} (p) is calculated from (3) using a shift z_v, equal to $z_a + 4.4$, where z_a is the shift already calculated for arterial blood. Then Sx_{O_2} is calculated from (1) using p, and Cx_{O_2} is calculated from (5) using the postulated actual Px_{O_2}.

APPENDIX 2

ACCURACY

If there is an error of y% shift in the calculated shift, then there will be a y% error in P_{95} and P_{90}. However, inspection of table I shows that this can lead to errors of up to about $2y$% in the calculated $C(\text{a}-x)_{O_2}$. Therefore, depending on what is regarded as a clinically acceptable error in $C(\text{a}-x)_{O_2}$, say 5%, 10% or 20%, the error in calculated shift must be limited to 2.5%, 5% or 10%. Errors in the measurement of Po_2 will produce equal percentage errors in the calculated shift. However, inspection of figure 4 shows that, at high saturations, identification of shift is much more sensitive to errors of So_2 than errors of Po_2. For example, changing from one curve to the next (a 5% shift) always requires a change of 5% of the Po_2 but, at an So_2 of 96%, it requires a change of only 0.5% saturation.

The problem becomes more acute as the So_2 increases towards 100%. Table III lists the maximum saturations at which a given accuracy of shift (errors of < 2.5%, < 5% or < 10% shift) can be achieved in the presence of a given error in the measurement of So_2 (0.1% to 2.0% saturation), neglecting any error in Po_2. For instance, if the error in measurement of So_2 is very small, say 0.1% saturation, then errors in shift will be limited to 2.5% shift (and hence errors in $C(\text{a}-x)_{O_2}$ to 5%) for So_2 values up to 98% saturation. On the other hand, with errors of 1% in the measurement of So_2 the error in shift at a saturation of 95% will be nearly 10% (and hence the error in $C(\text{a}-x)_{O_2}$ up to nearly 20%).

TABLE III. *Maximum saturations at which the error in the calculated shift of the dissociation curve will be less than 2.5%, 5% or 10% shift for various errors in measured saturation*

Measurement error (% saturation)	Maximum saturation for error in calculated shift to be less than: 2.5%	5%	10%
0.1	98.0	98.8	99.3
0.2	96.5	97.9	98.7
0.3	95.1	97.2	98.3
0.5	92.2	95.6	97.4
0.7	89.2	94.3	96.5
1.0	83.0	91.9	95.3
1.5	68.7	87.7	93.3
2.0	—	82.7	91.2

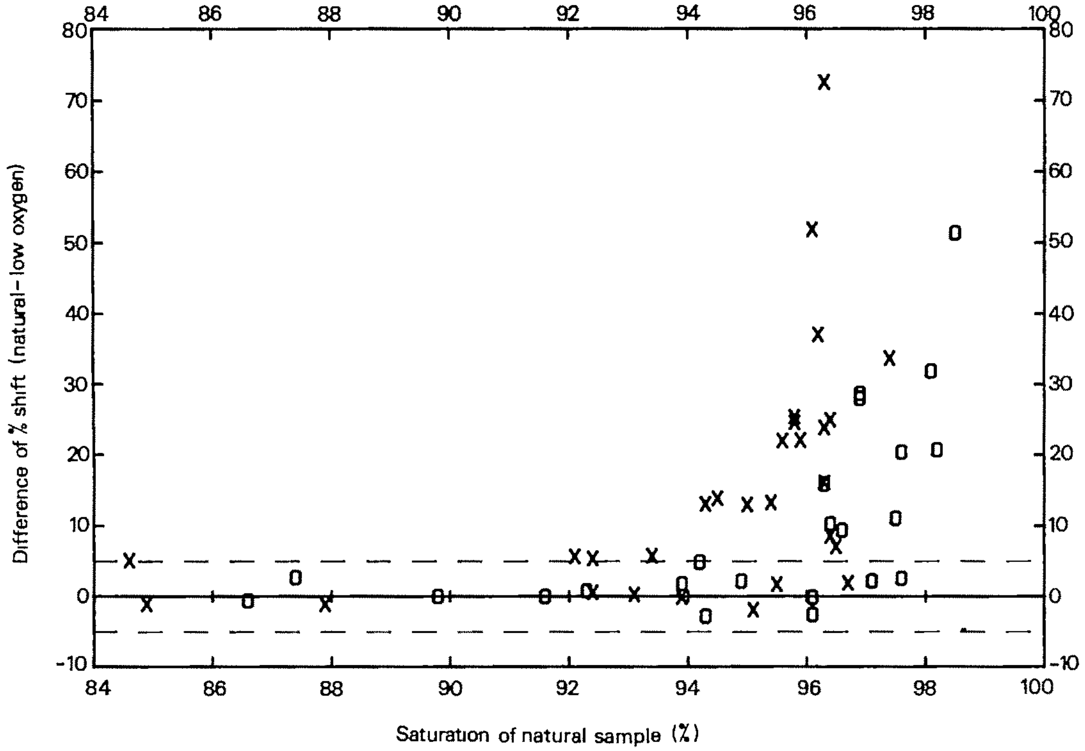

FIG. 6. Discrepancies between % shifts of the oxygen dissociation curve calculated from pairs of aliquots of routine samples of arterial blood. One aliquot was analysed as sampled, the other after equilibration with a low P_{O_2}, ~5 kPa. Batch 1 (○) equilibrated with a P_{CO_2} of 5.6 kPa; batch 2 (x) equilibrated with a P_{CO_2} similar to the value measured in the "parent" arterial sample. The analyses were performed using a Corning CO-oximeter M2500 and a Corning 178 blood-gas analyser. Each batch of analyses was spread over a few days, with an interval of a few weeks between the two batches.

The accuracy of measurement of saturation and tension will depend on the particular apparatus used. The Emergency Biochemistry Laboratory in the University Hospital of Wales uses a Corning "CO-oximeter" M2500 and a Corning 178 blood-gas analyser (Ciba Corning Ltd, Halstead, Essex). The manufacturer's instruction manuals claim accuracies of the order of 1–2% for both P_{O_2} and S_{O_2}, but these results include inaccuracies arising in the test procedure. Therefore we conducted an empirical test as follows.

From each of 52 routine blood samples coming to the laboratory, an aliquot was taken and equilibrated in an IL 237 tonometer (Instrumentation Laboratories (UK) Ltd, Warrington, Cheshire) (Chalmers, Bird and Whitwam, 1974) with a low P_{O_2}, resulting in saturations ranging from 61% to 87%, mean 73%. Both aliquots were analysed, and the % shift of the dissociation curve calculated from both sets of results. The measured P_{O_2} of the equilibrated, "low oxygen", aliquot was corrected for the measured differences of P_{CO_2} and pH from those of the "natural" aliquot according to a generalization of Kelman's (1966) equation (2):

$$P_{O_{2a}}/P_{O_{2b}} = 10^{\{0.024(t_a-t_b)-0.40(pH_a-pH_b)+0.06(\log P_{CO_{2a}}-\log P_{CO_{2b}})\}} \quad (6)$$

where subscripts $_a$ and $_b$ refer to the natural and low-oxygen aliquot respectively. (Temperature (t) was the same for both aliquots.)

The results are presented in figure 6 in terms of the difference of calculated % shift ("natural" minus "low oxygen") against the measured saturation of the natural sample. It can be seen that the differences are mostly within ±5% shift up to 94% saturation but that, at higher saturations, there is a systematic error and a large increase in scatter. Since the error in calculated shift at the low P_{O_2} will be small, and since the random component of that is *included* in the above ±5%, it seems reasonable to assume that, if calculations are restricted to samples with a saturation of no more than 94%, the calculated $C(a-x)_{O_2}$ will be accurate to ±10%.

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PROPRANOLOL INCREASES OXYGEN UTILIZATION DURING HYPOXIA

H. J. KHAMBATTA, J. G. STONE, J. ASKANAZI AND E. KHAN

SUMMARY

The effects of propranolol on whole body oxygen consumption and blood oxygen content were measured in the dog during extreme hypoxic conditions. At 9% inspired oxygen four of eight control animals died within 40 min. An identical second group was pretreated with propranolol and none died during the same hypoxic stress. Hypoxia decreased oxygen consumption in both groups, but the decrease was less in the propranolol-pretreated dogs. A second set of 16 dogs was ventilated with 10% oxygen and all animals survived. A similar, although less pronounced, effect on oxygen consumption was noted and propranolol once again lessened the hypoxia-induced decrease in oxygen consumption. With hypoxaemia, metabolic acidosis developed in all animals and the arterio–venous oxygen content difference decreased; however, propranolol lessened the acidosis and the decrease in arterio–venous oxygen content difference. We conclude that, during hypoxia, propranolol increases oxygen utilization by the tissues and this might account for better survival.

The oxygen stores of the body are limited, and the margin of safety during hypoxia is small. Hypoxia causes acidosis and the release of catecholamines from peripheral nerve endings and the adrenal glands (Von Euler and Lishajko, 1963; Hatcher and Jennings, 1966; Nahas et al., 1967). Increases in the concentrations of circulating catecholamines increase further the demand for oxygen and perpetuate the downhill spiral. β-Adrenergic antagonists compete for catecholamine receptor sites, and in normoxic patients—both with and without coronary artery disease—propranolol has been shown to inhibit stress-induced ischaemia by reducing myocardial oxygen consumption (Wolfson and Gorlin, 1969). Propranolol stabilizes cell membranes (Davis and Temte, 1968), and this protective effect may improve oxygen utilization and cell viability during hypoxia. The purpose of this study was to quantitate the effects of severe hypoxia on whole body oxygen consumption and oxygen utilization, and to determine whether propranolol, by altering these effects, might increase the margin of safety during hypoxia.

MATERIALS AND METHODS

Two series of investigations were performed. In the first, 16 mongrel dogs, average weight 12 kg, were given i.v. pentobarbitone 30 mg kg^{-1} and pancuronium 0.2 mg kg^{-1}. Anaesthesia and neuromuscular blockade were maintained thereafter with infusions of pentobarbitone 1.2 mg kg^{-1} h^{-1} and pancuronium, 0.2 mg kg^{-1} h^{-1}. This regimen results in a constant plasma concentration of pentobarbitone of 29.2 ± 1.1 µg ml^{-1} (unpublished observations), which provides satisfactory anaesthesia in the dog. The lungs were ventilated mechanically with a constant volume ventilator via a cuffed tracheal tube and a non-rebreathing system. A ventilatory rate of 10 b.p.m. was chosen and the tidal volume was adjusted to maintain a pHa of 7.4. Thereafter, the ventilator settings were not changed. The collection and analysis of expired and inspired gases has been described previously (Khambatta and Sullivan, 1974). Briefly, the expired gas was collected in a

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servospirometer (Model 220, Cardiopulmonary Instruments Corp., Houston, Texas), the timing of which was controlled by a computer real-time clock which utilized an analogue–digital interface and triggered solenoid valves. A gas mass spectrometer (MAT-M3, Varian Inc., Palo Alto, California) measured the concentrations of oxygen, carbon dioxide and nitrogen in the inspired and calibration gases, and in the collected expired gas as it was expelled from the spirometer. Data were analysed on-line by a digital computer (PDP/11, Digital Equipment Corp., Maynard, Mass.) which calculated minute ventilation ($\dot{V}$E), carbon dioxide elimination ($\dot{V}CO_2$), oxygen consumption ($\dot{V}O_2$) and respiratory quotient (R) after each spirometer cycle for the duration of the study. This method has been validated against expired gas samples collected in Douglas bags and measured by Scholander analysis (Herr et al., 1978).

Catheters were placed in the femoral and pulmonary arteries for blood sampling and pressure monitoring. Arterial and mixed venous blood were drawn into iced heparinized glass syringes and analysed immediately using a model 313 blood-gas analyser (Instrumentation Laboratory Inc., Boston, Mass.). Arterial and mixed venous oxyhaemoglobin saturation were determined from the Rossing and Cain nomogram (Rossing and Cain, 1966). Blood oxygen content was calculated using oxygen 1.38 ml/g Hb when fully saturated plus dissolved oxygen 0.003 ml/mm Hg PO_2 per 100 ml of blood. Cardiac index (CI) was calculated by the Fick principle, and systemic vascular resistance from standard formulae. Oesophageal temperature was monitored and maintained at 37 °C with the aid of a heating pad and infra-red lamps.

The dogs in the first series were randomly allocated to two groups with eight in each. In one group the lungs were ventilated with air for 1 h (control period) and then with a mixture of 9% oxygen and 91% nitrogen (hypoxic period) for 45 min at the same minute ventilation. At the end of the control period, and at 30 min into the hypoxic period, blood samples were obtained. The second group of animals were managed identically during the control period but, after sampling, received propranolol 1 mg kg^{-1} i.v. Thirty minutes later blood samples were collected, and these dogs were then ventilated with the same hypoxic mixture for 45 min. Blood samples were collected after 30 min of hypoxia. Because propranolol alters the oxygen dissociation curve, an appropriate modification of the calculated oxyhaemoglobin saturation was made (Pendleton et al., 1972; Agostoni et al., 1973).

Subsequently, a second series of 16 dogs (eight in each group, average weight 14 kg) was anaesthetized and ventilated as above. The design of this part of the investigation was identical except that the hypoxic mixture contained 10% oxygen and 90% nitrogen and propranolol 0.5 mg kg^{-1} was given to the treated group. A triple-lumen thermodilution pulmonary artery catheter (Swan–Ganz, Edwards Laboratories, California) was utilized for recording pressures, determining cardiac output and collecting mixed venous samples. Oxygen content in the arterial and mixed venous blood was measured directly with a Lex-O_2-Con-TL analyser (Lexington Instruments Corp., Waltham, Mass.). Oxygen consumption was calculated by the Fick principle, and systemic vascular resistance using the standard formulae.

Statistical analysis within the group was by paired t test; the survival rate between groups was by Chi-square with Yates' correction for continuity. A value of $P < 0.05$ was considered significant.

RESULTS

Table I contains data from the first series of 16 dogs in which oxygen consumption was measured directly. Of the eight dogs rendered hypoxic (9% inspired oxygen) without receiving propranolol, four died of circulatory collapse at 40 min. Even though the mortality rate was 50%, it did not achieve statistical significance ($P < 0.1$). There were no deaths in the propranolol-treated group. Hypoxia initially caused tachycardia and systemic and pulmonary hypertension in both groups. However, after 30 min of hypoxia, the untreated dogs demonstrated decreases in heart rate and mean arterial pressure with persistent pulmonary hypertension. In contrast, the propranolol-treated dogs were haemodynamically more stable and less acidotic when hypoxic. Hypoxia affected Pa_{O_2}, $P\bar{v}_{O_2}$ and CI similarly in both groups, but oxygen extraction, as calculated by arterio–venous oxygen content difference, was significantly greater in the propranolol-treated group. Oxygen consumption decreased substantially during hypoxia in both groups, but the decrease in the untreated group was significantly greater than in the propranolol-treated group.

TABLE I. *Summary of data (mean ± SEM) obtained in dogs breathing air, and an hypoxic mixture (9% oxygen) without and with propranolol pretreatment—first series.* * P > *0.01 compared with preceding value;* † P > *0.05 compared with preceding value;* ‡ P > *0.05 comparison of two hypoxic groups*

	Group 1 (n = 8)		Group 2 (n = 8)		
	Air	Hypoxia	Air	Air + propranolol	Hypoxia + propranolol
pHa	7.39±0.02	7.20±0.1*	7.39±0.02	7.38±0.02	7.25±0.01*‡
pH$\bar{v}$	7.33±0.02	7.16±0.01*	7.34±0.02	7.34±0.02	7.21±0.01*‡
Pa_{O_2} (kPa)	12.2±0.2	2.8±0.09*	12.4±2.4	12.7±0.3	3.1±0.09*
$P\bar{v}_{O_2}$ (kPa)	6.7±0.2	1.4±0.1*	6.7±0.1	7.3±0.3	1.6±0.1*
Pa_{CO_2} (kPa)	4.6±0.4	4.9±0.4	4.5±0.4	4.6±0.3	4.8±0.4
$P\bar{v}_{CO_2}$ (kPa)	5.2±0.4	5.4±0.5	5.1±0.4	5.1±0.4	5.3±0.5
$(Ca_{O_2}-C\bar{v}_{O_2})$ (vol%)	3.16±0.12	1.72±0.05*	3.12±0.13	3.53±0.08	2.17±0.15†‡
MAP (mm Hg)	124±10	103±9*	128±8	126±7	122±9‡
MPAP (mm Hg)	16±1	30±2*	15±1	17±2	22±2†‡
HR (beat min^{-1})	130±12	110±8†	127±10	109±8†	111±9
CI (litre m^{-2} min^{-1})	4.00±0.26	4.55±0.24	4.15±0.25	3.60±0.24	3.95±0.24
SVR (units)	29.75±1.45	21.54±1.89*	29.64±1.73	33.61±2.01	29.62±1.78‡
$\dot{V}o_2$ (ml m^{-2} min^{-1})	126.3±4.5	78.4±3.6*	129.6±4.9	126.9±5.2	85.7±3.8*‡
$\dot{V}co_2$ (ml m^{-2} min^{-1})	103.9±3.7	103.7±3.5	100.7±3.5	100.7±3.3	101.1±3.2
R	0.82±0.02	1.36±0.11*	0.78±0.02	0.80±0.02	1.20±0.06*‡
$\dot{V}_E$ (litre m^{-2} min^{-1})	5.19±0.25	4.99±0.29	5.43±0.31	5.43±0.33	5.57±0.29

Table II contains data from the second series of 16 dogs in which blood oxygen content and cardiac output were measured directly. There were no deaths in any of the untreated or propranolol-treated dogs when hypoxia was induced with 10% inspired oxygen. The initial response of both groups to the milder hypoxic stimulus was again tachycardia and hypertension but, at 30 min, although heart rate was significantly slower in the treated group, arterial pressure had returned to control in both groups. Pulmonary hypertension was less severe in the propranolol-treated group, although there was no significant difference between the two groups. Again, metabolic acidosis was more pronounced in the untreated dogs, even though hypoxia caused similar changes in Pa_{O_2} and $P\bar{v}_{O_2}$. Oxygen extraction, as measured by arterio-venous oxygen difference, was significantly higher in the propranolol-treated group and oxygen consumption decreased significantly more in the untreated group.

Similar changes were induced by both hypoxic

TABLE II. *Summary of data (mean ± SEM) obtained in dogs breathing air and an hypoxic mixture (10% oxygen) without and with propranolol pretreatment—second series.* * P > *0.01 compared with preceding value;* † P > *0.05 compared with preceding value;* ‡ P > *0.05 comparison of two hypoxic groups*

	Group 1 (n = 8)		Group 2 (n = 8)		
	Air	Hypoxia	Air	Air + propranolol	Hypoxia + Propranolol
pHa	7.40±0.01	7.24±0.01*	7.41±0.02	7.39±0.01	7.29±0.01*‡
pH$\bar{v}$	7.38±0.01	7.22±0.01*	7.38±0.02	7.36±0.01	7.26±0.02*‡
Pa_{O_2} (kPa)	12.7±0.4	3.9±0.2*	12.8±0.4	12.5±0.4	3.9±0.3*
$P\bar{v}_{O_2}$ (kPa)	6.1±0.1	2.7±0.2*	6.1±0.5	6.3±0.4	2.7±0.4*
Pa_{CO_2} (kPa)	4.7±0.4	5.0±0.4	4.6±0.4	4.6±0.4	4.8±0.3
$P\bar{v}_{CO_2}$ (kPa)	5.2±0.3	5.5±0.4	5.2±0.4	5.1±0.4	5.2±0.3
$(Ca_{CO_2}-C\bar{v}_{CO_2})$ (vol%)	3.4±0.1	2.5±0.09	3.4±0.2	3.9±0.4	3.2±0.14†‡
MAP (mm Hg)	125±8	123±9	127±9	125±8	128±9
MPAP (mm Hg)	15±1	23±2*	16±1	17±1	20±1†
HR (beat min^{-1})	128±10	130±9	130±8	110±9†	109±8‡
CI (litre m^{-2} min^{-1})	3.71±0.21	4.08±0.20	3.70±0.34	3.34±0.26	3.45±0.17
SVR (units)	32.01±2.25	28.92±1.76*	32.84±2.99	35.93±3.02	35.65±2.98‡
$\dot{V}o_2$ (ml m^{-2} min^{-1})	125.3±4.8	100.2±3.5†	123.3±4.6	124.0±2.4	111.1±2.0†‡

mixtures, although they were more pronounced when the inspired oxygen was 9%. Likewise, propranolol had the greatest effect during the more severe hypoxic stress.

DISCUSSION

Mild hypoxia has no measurable effect on oxygen consumption (Smith, Cooperman and Wollman, 1980), but a low inspired oxygen tension decreases it (Cain and Chapler, 1979). This work quantifies the magnitude of these changes in the dog when hypoxia is extreme. A 10% inspired oxygen concentration reduced whole body oxygen consumption by 20%, whereas 9% inspired oxygen caused a 38% decrease and death in half of the animals.

Hypoxia has been shown to induce various haemodynamic changes, depending upon the degree and the duration of hypoxia and the design of the study (Roberts, 1980). In dogs anaesthetized with chloralose–urethane and ventilated at a Pa_{O_2} of 3.73 kPa, bradycardia and hypertension were observed without a change in cardiac output (Kontos, Vetrovec and Richardson, 1970). Our surviving dogs, at a similar Pa_{O_2}, showed little change in arterial pressure, heart rate or cardiac output. However, the irreversible terminal events caused by severe hypoxia are usually bradycardia and hypotension (Cain, 1973). Half of our untreated dogs who were subjected to 9% inspired oxygen died in this manner at 40 min. The other half were more stable haemodynamically, even though all animals had a Pa_{O_2} of 2.8 kPa.

The acute administration of propranolol did not affect whole body oxygen consumption in this study. This absence of effect in normoxic dogs has been observed before (Khambatta, Chaffee and Sullivan, 1975; Cain and Chapler, 1979) even though myocardial oxygen consumption is consistently reduced in individuals with ischaemic and hypertensive heart disease (Wolfson and Gorlin, 1969; Sonnenblick and Frishman, 1981; Slogoff, 1983). Perhaps whole body measurements of oxygen consumption are too gross to detect changes in the heart, which consumes only 10% of the total under basal conditions.

Hypoxia is a stress which causes the release of catecholamines, the development of acidosis and eventual death (Von Euler and Lishajko, 1963; Hatcher and Jennings, 1966; Nahas et al., 1967). Propranolol improved the survival of animals that had severe acidosis and increased catecholamine concentrations in association with posthaemorrhagic shock (Berk et al., 1967; Halmagyi, Irving and Varga, 1968). Moreover, propranolol inhibited stress-induced myocardial ischaemia in patients with coronary artery disease (Wolfson and Gorlin, 1969). Their lessened symptoms and better survival were attributable to a reduction in myocardial oxygen consumption. Perhaps propranolol contributes to improved survival during hypoxia by reducing the wasteful demands of acidosis and increased oxygen consumption. Roberts and his colleagues (1976) found, as we did, that propranolol did not affect the usual circulatory response to hypoxia when the animals survived. Cain (1973) noted that severely hypoxic dogs treated with propranolol had a 19% longer survival time, but the findings were not statistically significant. Likewise, we found propranolol to be protective in the presence of severe hypoxia.

Pendleton and colleagues (1972) and Agostoni and co-workers (1973) showed *in vitro* that propranolol shifts the oxygen dissociation curve to the right. Oski and associates (1972) confirmed this rightward shift in man and found it to appear within 2 h of oral intake. They suggested that propranolol releases 2,3-DPG from the red cell membrane and lessens the affinity of haemoglobin for oxygen, thus increasing the availability of oxygen. In a study of patients with ischaemic heart disease, Schrumpf and colleagues (1977) showed that propranolol shifted the P_{50} from 3.75 to 4.23 kPa, although they were unable to demonstrate a change in 2,3-DPG concentration. A rightward shift of the oxygen dissociation curve has its maximum effect during normoxaemic conditions (Spector et al., 1977), when oxygen loading occurs on the high plateau of the dissociation curve and unloading occurs on the steep portion, allowing for increased oxygen extraction. During hypoxic hypoxaemia, however, the loading of oxygen occurs on the steep portion of the oxygen dissociation curve, severely diminishing loading and negating the potential benefit from increased unloading on the flatter low tail of the dissociation curve. Therefore, it is doubtful that we can fully attribute the increased arterio–venous oxygen content difference in the propranolol-treated hypoxic dogs to the rightward shift of the oxygen dissociation curve.

During hypoxia oxygen consumption was greater in the propranolol-treated dogs. This increased oxygen utilization, when the margin for survival was very narrow, could have been responsible for the improved survival in the propranolol-treated dogs. We can only speculate as to what was responsible for increased oxygen utilization. Propranolol is known to stabilize the cell membrane (Davis and Temte, 1968). Johannsson and Nilsson (1975) have shown that during acidosis the cell membrane is affected, leading to decreased calcium ion conductance. It may be that during hypoxia, in the presence of propranolol, cell membrane stability is preserved with improved cell survival and increased oxygen utilization. In the untreated dogs there was a significant decrease in systemic vascular resistance during hypoxia. Propranolol pretreatment, by preventing this decrease in total peripheral vascular resistance, could have resulted in a redistribution of blood towards vital areas such as heart and brain. If vital areas with higher oxygen demand receive more blood flow during hypoxia, oxygen utilization and survival should improve.

Carbon dioxide production did not decrease when oxygen consumption did and, therefore, there was an increase in respiratory quotient. However, oxygen consumption measured directly from minute ventilation and inspired and expired gases reflects only aerobic metabolism. During hypoxia, anaerobic pathways are utilized and the apparent imbalance is actually the result of carbon dioxide liberation from the bicarbonate pool as metabolic acidosis develops. The heart is an aerobic organ; that is, it relies almost exclusively on the oxidation of substrate for the generation of energy, and it can develop only a small oxygen debt (Braunwald and Sobel, 1984). The normal beating canine heart consumes oxygen at 8–15 ml min^{-1}/100 g (Rooke and Feigl, 1982). In the presence of hypoxia with concomitant acidosis and catecholamine release, there will not only be a further increase in the body's oxygen demand but also more anaerobic metabolism, thus limiting the oxygen available to the heart. Propranolol may work by reducing this dependence on anaerobic metabolism.

In summary, we have demonstrated that propranolol improves oxygen utilization and survival during hypoxic hypoxia. The mechanism of action, however, remains an enigma. Under these conditions the rightward shift of the oxygen dissociation curve is minor and two other possibilities remain. First, by occupying β-adrenergic receptor sites, propranolol alters the response of energy metabolism to hypoxia, which increases oxygen consumption, apparently as a whole-body stress response. This would seem to be a counterproductive mechanism which hastens cellular death. Second, by improving cell membrane integrity and perhaps blood flow to vital organs, propranolol may reduce cellular injury.

Roberts (1980) has aptly stated that "Hypoxia is a potential hazard during general anaesthesia and can not be ignored simply because it is considered that it should not occur." This study suggests a potential role for propranolol if the observations reported in the present study can be demonstrated to have clinical benefit.

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A MODEL OF THE EXTRADURAL SPACE AND A REAPPRAISAL OF THE EXTRADURAL SPACE PRESSURE

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SUMMARY

A model is described which was used to study the genesis of the pressure in the extradural space. It consists of a Perspex outer tube, with perforations covered with rubber septa to allow the insertion of needles, and Paul's tubing on the inside, representing the dura mater. The Paul's tubing is filled with water through a constant head of pressure apparatus. The response of the model to the insertion of an extradural needle and the reproduction of various clinical phenomena are described. The pressure in the extradural space is discussed in relation to the performance of the model.

Although the existence of a pressure in the extradural space has been acknowledged for 60 years, the cause of this phenomenon is disputed. The following proposals have been advanced to explain the genesis of the extradural space pressure:

(1) The negative pressure in the extradural space is an artefact, which is caused by dural dimpling (Janzen, 1926; Bonniot, 1934; Eaton, 1939).

(2) The negative pressure in the extradural space is an artefact, which is caused by the retraction of the ligamentum flavum around the epidural needle (Zarzur, 1984).

(3) The negative pressure is the result of transmission of the negative intrathoracic pressure through the intervertebral foramina into the extradural space (Zorraquin, 1936; Macintosh and Mushin, 1947; Macintosh, 1950).

(4) The negative pressure is attributable to the disproportionate growth of the vertebral canal compared with the dural sac (Heldt and Maloney, 1928).

(5) The negative pressure is a temporary phenomenon caused by stretching the dura mater when the back is flexed (Odom, 1936).

(6) The pressure changes in the extradural space are related to changes in the cerebrospinal fluid pressure, causing the dural sac to bulge, thereby producing a positive pressure, or to collapse, producing a negative pressure (Bryce-Smith, 1950).

(7) The positive pressure is produced by the transmission of the pressure in the subarachnoid space through the dura mater to the extradural space (Shah, 1981).

The existence of so many theories for the genesis of the extradural space pressure raises two important questions. First, what do clinicians mean when they describe the pressure in the extradural space and, second, which of these theories, if any, explains adequately the genesis of such a pressure? A model of the lumbar spinal canal, which could be used *in vitro* to reproduce some of the changes which have been recorded *in vivo*, has been designed and studied, in an attempt to arrive at an answer to these questions.

MATERIALS AND METHODS

The model comprised two parts. The outer shell, corresponding to the vertebral canal, was a Perspex cylinder, at various points along which holes had been drilled and covered with rubber septa to allow the insertion of needles. The inner layer, corresponding to the dural sac, was Paul's tubing. The top end of the Paul's tubing was everted over the end of the Perspex outer tube, and a bung inserted, through which ran a tube connected to a constant pressure device providing a pressure of 18 cm H_2O. The bottom end was tied off, and a bung inserted to the bottom of the Perspex tube (fig. 1). The inner tube was filled

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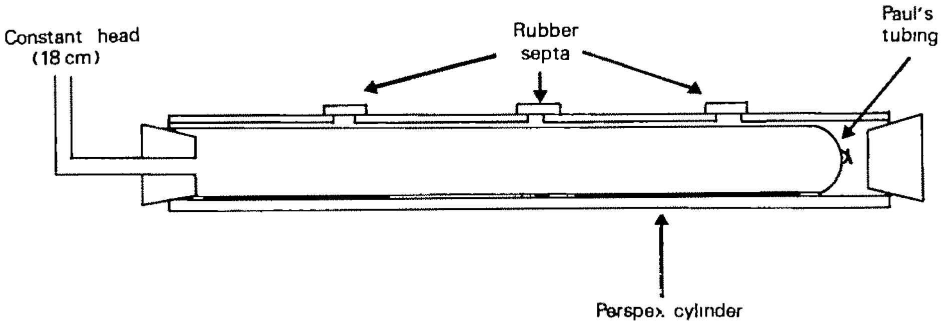

FIG. 1. Model of the extradural space.

with water, representing the cerebrospinal fluid (CSF); the layer between the inner and outer tubes represented the extradural space.

The changes in pressure on inserting an epidural needle were measured. A Tuohy needle was attached directly to the dome of a transducer, both being filled with water. The needle was inserted through the rubber septum, and the pressure changes measured, both at the needle, and at other points in the "extradural space". The pressures were recorded using a Bell and Howell transducer (type 4-327-1221) and an Elcomat multichannel u.v. recorder.

Subsequent tests were designed to reproduce the findings of other authors. Two methods used to define the extradural space—the hanging drop technique of Guttierez and the Macintosh balloon—were tested. For the hanging drop test, the Tuohy needle was inserted to the septum so that the tip was covered, and enough water was inserted to the hub of the needle to create a hanging drop. The needle was then pushed into the "extradural space", and the effect on the hanging drop was observed. The pressure inside the Paul's tubing was then altered by varying the height of the constant head of pressure apparatus, and the effect on the hanging drop noted.

With the Macintosh balloon, the balloon was connected to the Tuohy needle by a four-way tap, the third arm of which was connected to a transducer of the type described above by a short length of narrow-bore tubing. Both the tubing and the dome of the transducer were filled with water. With the tip of the needle in the septum, 2 ml of air was injected to the balloon, and the pressure within the balloon measured. The needle was then advanced until it entered the "extradural space". The new pressure was recorded. The effect of altering the pressure within the Paul's tubing, as described above, was noted.

Finally, a Portex epidural catheter was inserted to the "extradural space" and 0.5 ml of water was injected to the catheter, which was then held vertically as described by Shah (1981). The height of water in the catheter above the point of insertion was measured. This initial manoeuvre was repeated until a constant level could be recorded. This procedure was performed with the model in both the horizontal and upright positions.

RESULTS

When the Tuohy needle was inserted, there was a decrease in pressure to -30 cm H_2O, with the needle inserted 5 mm to the "extradural space". The pressure returned to zero when the needle was withdrawn. Indentation of the Paul's tubing was noted. All pressure changes recorded were found to be independent of the position of the model. Whilst these changes were recorded, there were no changes noted in the pressure in the "extradural space" at other points along the tube.

The two methods used to define the extradural space responded as they have been observed to do in the clinical situation. With the hanging drop technique, insertion of the needle to the "extradural space" caused the hanging drop to disappear into the hub of the needle. The drop could then be made to oscillate backwards and forwards by cyclically varying the pressure of the water inside the Paul's tubing. The Macintosh balloon responded in a manner similar to that seen in clinical practice. When the tip of the needle was in the septum, the balloon remained expanded, but it collapsed immediately the tip of the needle entered the "extradural space". The balloon could be made to re-expand partly when the pressure in the Paul's tubing was increased. The initial pressure recorded in the balloon was 47 cm H_2O. When the pressure inside the "extradural space" was measured after the Macintosh balloon had deflated, it was found to be 16 cm H_2O.

In the final test when the epidural catheter was used as a water manometer, the water level initially decreased rapidly, producing a pressure of only 2 cm H_2O. However, when the test was repeated the pressure was found to increase on each occasion until a limiting pressure was produced. The limiting pressure produced was dependent on the position of the model, but in all measurements made the value was 1 cm H_2O less than the hydrostatic pressure at the position of the catheter tip.

DISCUSSION

The four different clinical techniques assessed in the model behaved as they do *in vivo*. Insertion of the Tuohy needle produced a negative pressure, which was associated with indentation of the Paul's tubing. The greater the indentation, the greater the change in pressure, a fact which accords with the findings of Janzen (1926) and Eaton (1939), and suggests that the negative pressure is caused by the distortion of the dura mater. This also confirms the findings of Aitkenhead and colleagues (1979), who demonstrated that dural dimpling occurred in dogs, and showed that the negative pressure was a function of the amount of dural displacement. Evidence of dural dimpling in man was provided by Orrison, Eldevik and Sackett (1983), who demonstrated this phenomenon whilst performing cervical myelograms.

The Macintosh balloon could be made to re-inflate partially by increasing the pressure in the Paul's tubing and, similarly, the hanging drop could be made to oscillate with fluctuations of the pressure of the Paul's tubing. These findings agree with those of Macintosh (1950), but they do not confirm his belief that the pressure in the extradural space is dependent upon the pressure in the thoracic cavity. It is more probable that the changes he noted with ventilation were related to changes in the CSF pressure secondary to ventilation.

Initially, repeating the work of Shah (1981) gave rise to results which differed from his. The production of such a low pressure may be related to the presence of a space between the rubber septum and the Paul's tubing, which has to be filled with fluid before any measurement can be made, and this will accommodate 0.5 ml of water. However, continuing to fill the "extradural space" with water will produce a situation similar to the extradural space compliance tests of Bengis and Guyton (1977), which will produce an extradural space pressure tending towards the pressure within the lumbar CSF, but not reaching it, as a result of part of the pressure being responsible for keeping the dural sac distended. Thus, regardless of the position of the model, the height of the water in the extradural cannula will approximate to, but can never equal, the pressure within the Paul's tubing. A similar situation was produced with the experiment using the Macintosh balloon.

Although it has been shown that these clinical phenomena can be reproduced *in vitro*, the limitations of the model must be taken into account. This model was designed to be simple, and therefore cannot be as detailed in its construction as the lumbar spine. The Paul's tubing was not attached to the inside of the Perspex outer tube at any point other than at one end—a difference from the situation *in vivo* (Parkin and Harrison, 1985). The closed end of the Paul's tubing was free within the outer tube—although this situation was not totally dissimilar to that in the body, where the end of the dural sac is free to move up or down to a limited extent (Martins, Wiley and Myers, 1972). One notable absence in this model was the internal vertebral venous plexus. This may play a role in determining the pressure in the extradural space, but it was considered difficult to design a component of this model which would correspond to this venous plexus.

It is suggested that the pressure being measured in the extradural space *in vivo* is not the pressure native to the extradural space, but an artefact created by the introduction of a needle or catheter—a conclusion reached by Janzen in 1926. Furthermore, it is suggested that the pressure measured in the extradural space is an artefact of the method used to measure it. Thus if a needle which causes the dura to be displaced away from the walls of the vertebral canal is inserted, the pressure recorded will be negative on the condition that no air is allowed to enter. On the other hand, if a catheter is inserted to the extradural space, and fluid is allowed to enter, the pressure recorded will be related to the pressure between the dural sac and the vertebral canal. These findings support both Janzen's (1926) and Shah's (1981) theories for the genesis of the pressure in the extradural space.

It is the author's opinion that the pressure in the extradural space is not a single measurable entity, but a complex dynamic equilibrium of forces which exist between the vertebral canal, the contents of the extradural region, and the dural sac. Because of this it might be better if performers of extradural injections were to content themselves with the fact that various clinical phenomena exist, which they can use to their advantage, rather than to attempt to create a holy grail out of the pressure in the extradural space.

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HEAT AND MOISTURE EXCHANGERS IN ARTIFICIAL VENTILATION

An Experimental Study of the Effect of Gas Leakage

S. E. TILLING AND B. HAYES

SUMMARY

The effect of gas leakage around an uncuffed tracheal tube on the performance of Heat and Moisture Exchangers (HME) was examined experimentally. Such leaks were shown to cause measurable decreases in the humidity output and efficiency of HME. The magnitude of the decrease in humidity output was shown to be dependent upon the proportion of expired volume which was leaked, and on the inspired volume. Other factors are discussed.

Humidification of inspired gases during spontaneous breathing and artificial ventilation is well established (Chamney, 1969; Boys and Howells, 1972; Weeks, 1975; Chalon et al., 1979, 1981) and a variety of humidifiers is available (Sara, 1965; Sara and Currie, 1965; Hayes and Robinson, 1970; Reynolds, 1974; Weeks, 1975; Hayes, 1978). A less expensive method is the use of heat and moisture exchangers (HME)—which conserve humidity (Toremalm, 1960; Mapleson, Morgan and Hillard, 1963; Shanks and Sara, 1973; Steward, 1976; Walker and Bethune, 1976; Oh, Thompson and Hayward, 1981; Weeks, 1981), possibly with fewer hazards than have been encountered with heated humidifiers (Klein and Graves, 1974; Bancroft, 1982), and with the advantage that electrical or gas power is not required for their operation. Although possible and actual drawbacks have been described (Buckley, 1984; DHSS, 1986), HME have become increasingly popular and have supplanted heated humidifiers in some instances (Bethune and Shelly, 1985). HME relying on condensation–evaporation alone have been evaluated (Walker and Bethune, 1976; Oh, Thompson and Hayward, 1981; Weeks, 1981; ECRI, 1983), as have others which have hygroscopic additives (Gedeon and Mebius, 1979; Revenas and Lindholm, 1979; Hay and Miller, 1982; Stoutenbeck, Miranda and Zandstra, 1982) and also one which is claimed to be hydrophobic (Bethune and Shelly, 1985).

The performance of HME is generally less flexible, and of a lower order of efficiency, than that of heated humidifiers. They have, nevertheless, been found satisfactory in clinical practice, even though their water output has been confirmed (Weeks and Ramsey, 1983; Ogino, Kopotic and Mannino, 1985) as being less than had formerly been thought necessary for adult patients (Editorial, 1979). Moreover, a recent report suggested that an adult HME modified for neonatal application was satisfactory in use (Duncan, 1985) and since then a purpose-designed neonatal HME has been introduced (ICOR AB, Sweden).

HME have been used with continuous positive airway pressure (CPAP) and positive end-expiratory pressure (PEEP), the latter often accompanying artificial ventilation in adults, children and neonates. During the artificial ventilation of neonates it is customary to use a tracheal tube the diameter of which is, by intention, smaller than that which would fit snugly at the level of the cricoid cartilage (Sweeney, Allen and Steven, 1973), in order to avoid trauma to the mucosa, local mucosal swelling and stenosis after removal (Allen and Steven, 1965, 1972; Stocks, 1966; Markham, Blackwood and Conn, 1967; Owen-Thomas, 1967; Abbott, 1968; Hatch, 1968).

We investigated the effect of the inevitable leak

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around the tracheal tube on the performance of the HME by devising an investigation in which a lung model was ventilated by intermittent positive pressure ventilation (IPPV) at tidal volumes and frequencies of ventilation encountered in clinical practice. Leaks, which simulated those associated with ventilation through a tracheal tube forming an imperfect seal at the level of the cricoid cartilage, were permitted.

MATERIALS AND METHODS

The test apparatus was arranged as shown in figure 1. A Barnet Mk III ventilator (Philips Medical Ltd) was used to ventilate a Lung Ventilator Function Analyser (LVFA) (Medishield Limited) which was maintained at a temperature of 37 °C by immersion in a water bath. The gas inside the LVFA was humidified by the addition of a small quantity of water before the start of the tests, and saturation in the static condition was confirmed by measurement before and after each test. A flow splitting valve was interposed between the HME and the LVFA to separate the inspired and expired gas flows, as described by Weeks (1974). Humidity and temperature were measured continuously in the inspiratory and exiratory limbs of the valve, by hygrometers ("Si-grometer", Moisture Control and Measurement Ltd) and Type K Cr/Al thermocouples (Kane and May Ltd).

Previous work had confirmed the suitability of the hygrometer for the measurement of breathing system humidity (Tilling, Hancox and Hayes, 1983). The measurements represented the inspired and expired humidities and temperatures in the test system.

The inflow and outflow gas streams were separated in order to overcome the limitations imposed by the response times of both humidity and temperature sensors (Berger and Balko, 1973). The outputs from the temperature and humidity sensors were taken to a microcomputer (Commodore Business Machines Model 4032)

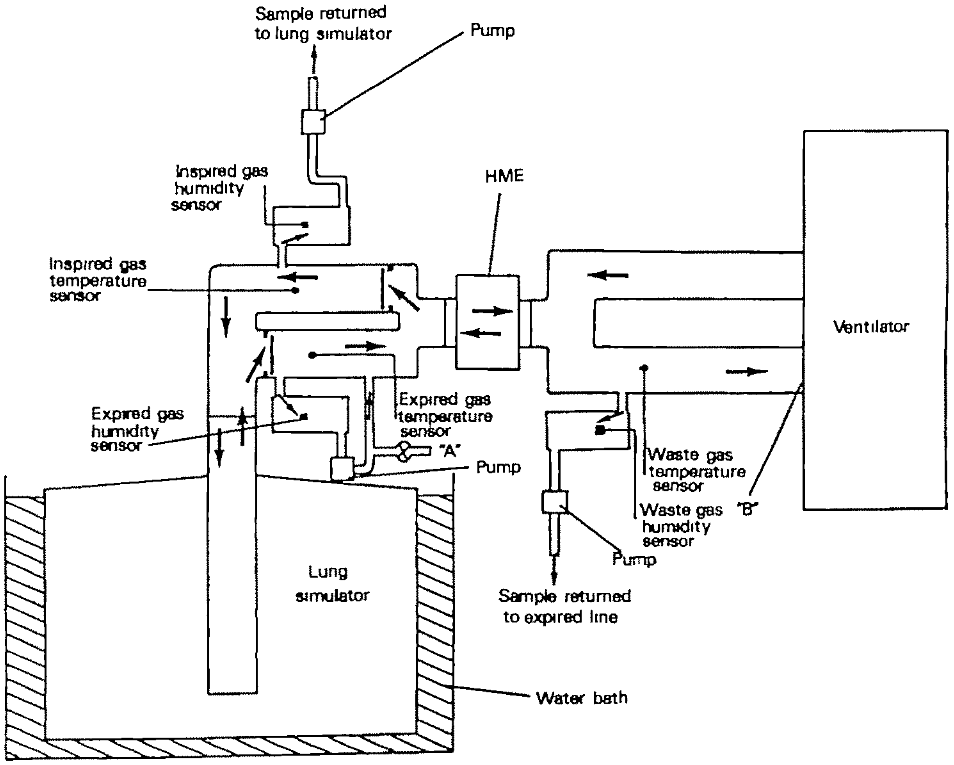
Sample returned to lung simulator
Pump
Inspired gas humidity sensor
HME
Inspired gas temperature sensor
Ventilator
Expired gas humidity sensor
Expired gas temperature sensor
"A"
Pump
Waste gas temperature sensor
Waste gas "B" humidity sensor
Pump
Sample returned to expired line
Lung simulator
Water bath

FIG. 1. Diagram of test apparatus showing lung ventilator function analyser (lung simulator) and the positioning of the transducers in the flow splitting valve. To simulate a leak around the uncuffed tracheal tube, a leak was introduced at the valve A.

TABLE I. *Details of four tests in which a Lung Ventilator Function Analyser was ventilated through an adult Heat and Moisture Exchanger, without and with a leak between the two pieces of equipment*

Test	Frequency (b.p.m.)	Measured tidal volume (ml ± 2 %) Before leak	After leak	Leak (% ± 4)
1	25	54	40	25.9
2	25	195	168	13.8
3	25	226	184	18.5
4	25	460	405	11.9

via an analogue-to-digital converter (AIM 16, Connecticut Computer Inc). Measurements were made every 30 s for the duration of each test.

The LVFA was ventilated through an adult HME (Engstrom "Edith", Gambro Ltd), without a leak, at the frequencies shown in table I. After 30 min a leak was introduced at point A (fig. 1) to simulate the leak around a tracheal tube. A Wright mechanical respirometer was used to measure the "expired" gas volume before and after the introduction of the leak, thus enabling the proportion of expired gas escaping to be derived. The respirometer was placed at the point of entry of the expiratory limb of the breathing system to the ventilator, to avoid problems associated with condensation.

RESULTS

Four tests were conducted with a leak between the HME and the LVFA. In each case the leak was introduced after 30 min and the test continued for a further 30 min. The ventilator settings are shown in table I. The errors quoted in the table are based on an uncertainty of ±2 % in the reading of the respirometer, as quoted in the manual supplied with the respirometer.

The variations in inspired and expired humidity with respect to time are displayed graphically in figures 2–5. The results, summarized in table II, show the mean values of humidity before and after the introduction of a leak. Each result is the mean (±1 SD) of 60 readings.

DISCUSSION

The validity of using a lung model which does not maintain constant humidity in the expired gas under all conditions will be contested, but the matter can only be settled by making measurements on patients. The figure for energy loss in expired breath of normally breathing adults, published by Walker, Wells and Merrill (1961), was compared with the results of tests 1–4. In our model, the rate of energy loss in the expired breath was found by adding together the power passed to

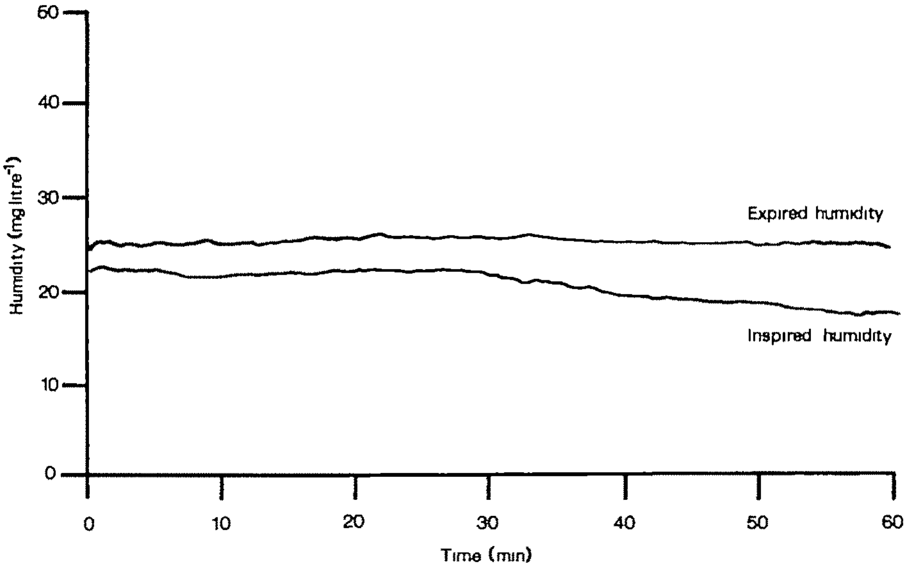

FIG. 2. Inspired and expired humidity with inspired tidal volume of 54 ml and a 25.9 % leak at the tracheal tube after 30 min.

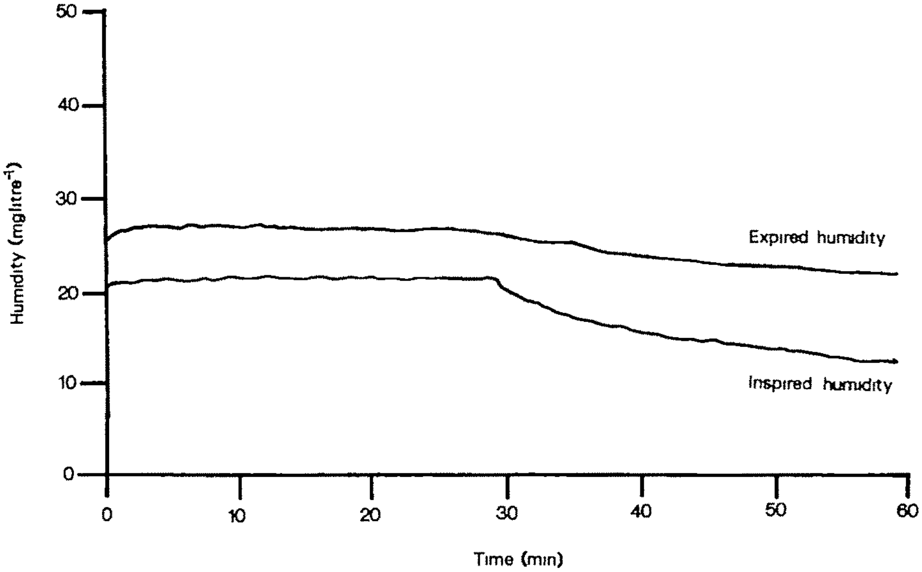

FIG. 3. Inspired and expired humidity with an inspired tidal volume of 195 ml and a 13.8% leak at the tracheal tube after 30 min.

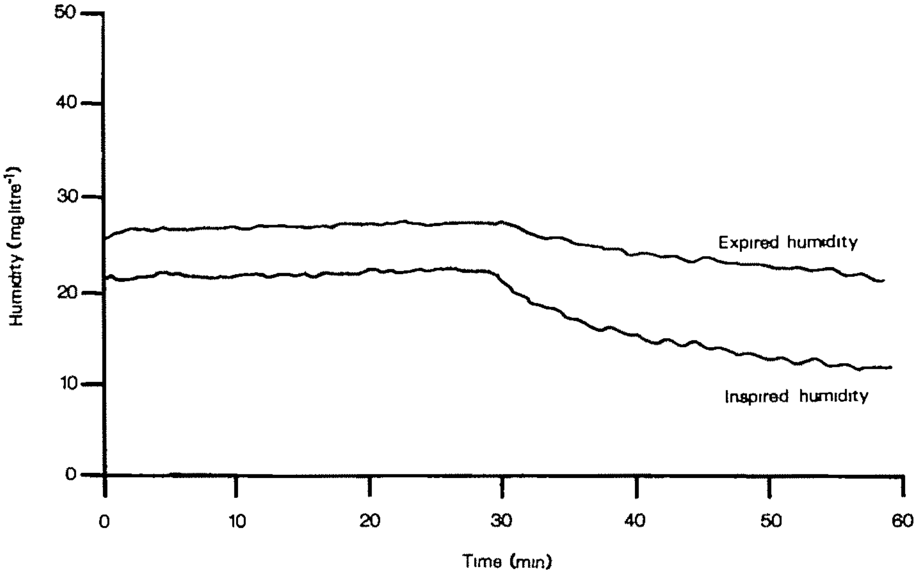

FIG. 4. Inspired and expired humidity with inspired tidal volume of 226 ml and an 18.5% leak at the tracheal tube after 30 min.

the HME and the power lost to the room (table III). Walker and colleagues quote a net loss from the respiratory tract of "about" 16.9 W, which is of an order comparable to the power losses measured in our tests of 2.24 W, 7.56 W, 8.89 W, 19.81 W for tests 1, 2, 3 and 4, respectively.

The tidal volume settings were chosen to cover the ranges expected in small paediatric, and adult, practice. The results in table II show that the standard deviation is greater after the introduction of a leak than previously. The reason is apparent in the continuous recordings of humidity. In all cases, whereas inspired humidity was constant for the first 30 min of test, it decreased steadily during

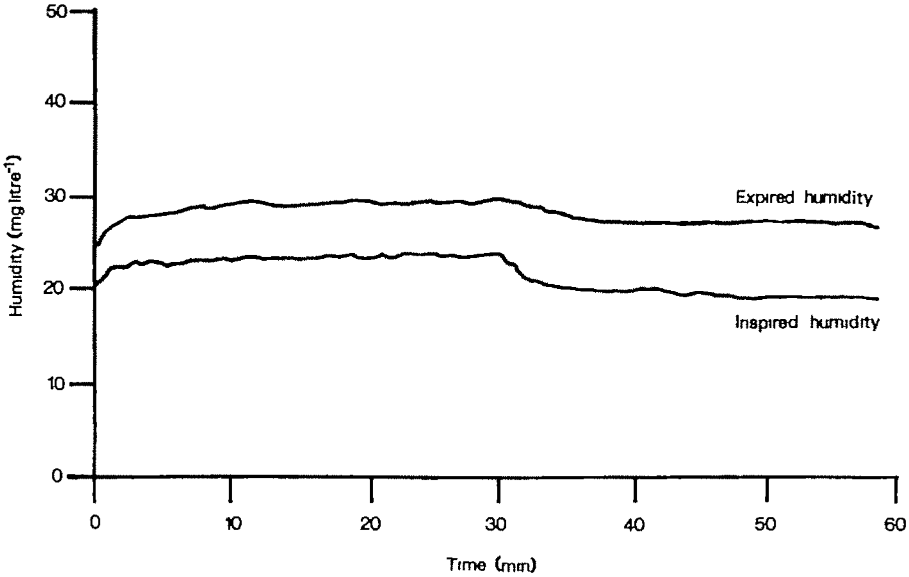

FIG. 5. Inspired and expired humidity with inspired tidal volume of 460 ml and an 11.9% leak at the tracheal tube after 30 min.

TABLE II. *Results: mean values of humidity before and after the introduction of a leak*

			Before leak		After leak	
Test	Initial V_T (ml)	Leak (%)	Mean inspired humidity (g m^{-3})	Mean expired humidity (g m^{-3})	Mean inspired humidity (g m^{-3})	Mean expired humidity (g m^{-3})
1	54	25.9	21.89±0.2	25.87±0.34	19.09±1.23	25.38±0.34
2	195	13.8	21.34±0.23	26.62±0.37	14.95±2.15	23.39±1.24
3	226	18.5	22.06±0.31	26.86±0.53	15.11±2.47	24.00±1.42
4	460	11.9	23.31±0.61	28.59±0.89	19.82±1.16	27.24±0.81

TABLE III. *Rates of energy transfer (power) to the patient, the HME and the atmosphere, and losses to the HME and atmosphere expressed as percentage of total available power*

Test	Power to patient (W)	Power to HME (W)	Power loss to room (W)	Power losses (%)		
				To room	In HME	Total
1	1.9±0.04	1.66±0.04	0.58±0.02	25.9±1.6	−14.5±2	11.4±2
2	5.87±0.13	6.51±0.15	1.05±0.04	13.9±0.9	9.8±4	23.7±5
3	6.85±0.15	7.24±0.16	1.65±0.07	18.6±1.3	5.3±4	23.8±5
4	15.84±0.35	17.41±0.40	2.40±0.10	12.1±0.8	9.0±4	12.1±5

the latter part of the test when the leak was present. Thus, it appears that when an HME is used instead of a conventional heated humidifier in a breathing system in which there is a gas leak around the tracheal tube, the inspired humidity is lower than would be expected from manufacturers' data or from the results of tests in which no leak has been simulated.

The largest leak in terms of proportion of initial tidal volume occurred in test 1; that is, with the smallest tidal volume (54 ml) selected. In this instance, there were only small decreases in values of inspired and expired humidity. The greatest decrease in humidity was obtained in tests 2 and 3 with tidal volumes of 195 ml and 226 ml, whereas the largest tidal volume (460 ml) produced a relatively smaller decrease in inspired humidity on the introduction of a leak of some 12%.

The results demonstrate that a leak between the HME and the LVFA causes a decrease in the humidity of the inspired gases. In figures 2–5 the differences in humidity between the inspired and expired gases were related to the "efficiency" of the HME. The two characteristics diverge after the introduction of a leak—revealing decreasing efficiency.

In the case of the smallest tidal volume (54 ml), expired humidity was unaffected by the leak, even though the inspired humidity decreased. To explain this it is suggested that, with very small tidal volumes, the LVFA may be able to make good humidity and temperature losses from its own reserves; that is, water vapour has time to diffuse from within the LVFA and increase water vapour pressure of the incoming gas before it is expired. Therefore, the temperature and humidity of the expired gas remain unaltered (i.e. its specific energy–energy per unit volume is the same, see Appendix). With larger tidal volumes there is insufficient time for the LVFA to saturate the incoming gas. Therefore, expired gas humidity and temperature decrease, compounding the effects of lower energy release in the HME.

Table III shows the power (or rate of energy transfer) to the HME, that returning to the patient and that lost to the atmosphere. Values were calculated from the results (see Appendix) for humidity and temperature shown in table III, using well-established thermodynamic relationships (Goff and Gratch, 1946; Goff, 1949; Institution, 1973; Institute, 1975). The errors quoted are based on the combined random errors in temperature, humidity and flow measurements.

In this table, the power losses to the surrounding atmosphere and those in the HME are shown as percentages of the total available power. The large errors in these results are attributable to the small volumes being measured and the small differences between the tidal volumes measured before and after the introduction of the leak. The percentage power losses to the surroundings are the same as the percentage volume losses from the system.

An interesting result of test 1 (using the smallest tidal volume of 54 ml) was the return of more energy to the LVFA from the HME than was delivered from the LVFA to the HME. This can only be explained by assuming that energy from the surroundings was utilized by the HME or that an exothermic chemical reaction in the hygroscopic additive had a significant effect. In either case, this went some way towards offsetting the proportionally very large power loss to the surroundings in this test (25.91%), and to reducing the overall power loss to 11.4%. Thus, it may be inferred that, in different ambient conditions or when an HME with a hygroscopic additive is not being used, the power loss could be worse, thereby leading to a greater decrease in the humidity of the inspired gas. In the other three tests losses in the HME were additional to those resulting from leakage of gas. Tables II and III clearly demonstrate that the total power loss was related to the observed decrease in the humidity of the inspired gas. The largest decrease in the humidity of the inspiratory gas was seen in the results of tests 2 and 3 (table II), which had the highest total power loss (table III).

CONCLUSION

When an HME is included in a breathing system with an uncuffed tracheal tube and, especially, if the tube is substantially smaller than that permitted by the cricoid opening, the inspired humidity may be reduced. The results indicate that the magnitude of the reduction is affected by the proportion of the inspired volume which escapes from the tracheal leak and by changes in the inspired tidal volume. We suggest that ventilatory frequency, environmental conditions and the type of HME used (hygroscopic or non-hygroscopic) may also have important effects. More specific tests would be needed to establish mathematical correlations between any of these factors and the reduction of inspired humidity.

Calculations of power loss reveal that, in terms of energy loss from the patient, the effect of the leak around the tracheal tube is unimportant, amounting to between only 14% and 35% (i.e. power loss to room from table III, as a percentage of the total power loss in the expirate). However, the losses are superimposed on losses resulting from the donation of energy to inspired gases, if these are not supplied at the required energy level.

The principal effect of the energy loss by way of the leak is that on HME performance and, hence, on the humidity of the inspired gas. This, in turn, may be expected to cause greater energy loss from the respiratory mucosa than would otherwise be the case.

APPENDIX

An HME can only conserve as much of the patient's own heat and moisture as is delivered to it in the exhaled breath. It is convenient to think of this as the energy contained in the gas as a result of its moisture content and temperature. A gas with a given humidity and temperature has an energy content specified by that humidity and temperature which may be expressed in J/kg of gas, and this energy content, called enthalpy, can be calculated or obtained from tables. If a proportion of this energy bypasses the device (that is, if it passes directly to the atmosphere around the outside of the tracheal tube) then the energy which escapes is no longer available to be conserved.

The enthalpy is a measure of the total energy which is available in the gas. A substance has a certain finite amount of energy at any temperature including absolute zero, but in order to make calculations uniform the zero point (datum) of enthalpy is usually taken as 0 °C. Specific enthalpy (h) of a moist gas is equal to the sum of the enthalpy of the air and the enthalpy of the water vapour:

$$h = ha + g.hg \tag{1}$$

where h = total specific enthalpy (J $\mathrm{kg^{-1}}$), ha = specific enthalpy dry air (J $\mathrm{kg^{-1}}$), hg = specific enthalpy water vapour (J $\mathrm{kg^{-1}}$) and g = moisture content of the air (kg $\mathrm{kg^{-1}}$).

At constant pressure the enthalpy values are functions of the temperature of the air and water and these values can be found in tables or calculated (Institution, 1973).

The total energy of a given mass of gas is then easily calculated:

$$E = h \times m \tag{2}$$

where E = energy (J), h = specific enthalpy (J $\mathrm{kg^{-1}}$) and m = mass of gas (kg), or from a given volume:

$$E = h \times d \times v \tag{3}$$

where h = specific enthalpy (J $\mathrm{kg^{-1}}$), d = gas density (kg $\mathrm{m^{-3}}$) and v = gas volume ($\mathrm{m^3}$).

It is evident from examination of equations (2) and (3) that the total energy may be varied by adjusting the mass (m) or volume (v) while maintaining the specific enthalpy at a constant value.

Power loss (rate of energy transfer) is calculated:

$$P = h \times v \times d \tag{4}$$

where P = power (W), h = enthalpy (J $\mathrm{kg^{-1}}$), v = volume flow ($\mathrm{m^3\,s^{-1}}$) and d = density (kg $\mathrm{m^{-3}}$).

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Br. J. Anaesth. (1987), 59, 1189–1191

WHICH pH PAPER?†

A. CHAFFE

SUMMARY

Five different brands of pH indicator paper were used by 20 anaesthetists to test four buffer solutions. There were significantly fewer correct answers with two papers than with the other three. The worst paper in the study (Whatman full range) gave only 20% correct answers, compared with 92.5% from the best (Merck).

In anaesthetic practice it is occasionally necessary to make a rapid and accurate measurement of the pH of the gastric contents. A simple and convenient method is to use paper impregnated with a suitable indicator, the change in colour being read against a comparison chart provided with the paper.

The purpose of this study was to compare the accuracy of interpretation of five different indicator papers when used by anaesthetists to test the pH of buffer solutions in the clinically important pH range 2–6.

MATERIALS AND METHODS

Five different indicator papers were assessed (table I), each taken from stock in current use within the hospital.

Four buffer solutions of pH 2, 3, 4 and 6 were made up in the quality control section of the hospital pharmacy. The pH of each was verified again at the conclusion of the investigation to ensure that no significant alteration had occurred during testing.

Each anaesthetist tested four solutions with each of the five indicator papers, with the jars rearranged between each paper. The results were recorded by a separate observer to remove any bias. Twenty anaesthetists participated in the study; none was colour-blind. The readings were taken with glasses, if worn, against a white background.

TABLE I. *The indicator papers tested*

Indicator paper					
No.	Brand	pH range	Number of colours	Special instructions	Cost
1	Camlab	1–11	Three	None	£4.80/reel £4.05/refill
2	Whatman	1–14	One	Read at 30 s	£5.10/4 reels
3	Merck Acilit	0–6	Three	Check while still moist	£3.50/100 strips
	& Neutralit	5–10	Three		
4	Whatman (BDH)	1–5	One	Read at 30 s	£5.10/4 reels
	Narrow range	3–7	One		£5.30/4 reels
5	Whatman Universal	1–11	One	None	£3.85/4 books

The results were analysed using the Chi square test.

RESULTS

No solution had deteriorated during the period of the investigation (table II).

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†Study carried out at St James's Hospital, Leeds 9.

TABLE II. *Buffer solutions composition and pH check. All buffers were McIlvaine Buffers. The pH meter was a Radiometer 26 standardized against pH 7·0 and 4·0 buffers*

Solution	Composition	pH before testing	pH after testing
pH 2	Citric acid monohydrate 2.058 g Disodium hydrogen Orthophosphate anhydrous 0.057 g Distilled water to 100 ml.	1.90	2.00
pH 3	Citric acid monohydrate 1.668 g Disodium hydrogen Orthophosphate anhydrous 0.584 g Distilled water to 100 ml.	2.83	2.90
pH 4	Citric acid monohydrate 1.290 g Disodium hydrogen Orthophosphate anhydrous 1.095 g Distilled water to 100 ml.	3.98	4.03
pH 6	Citric acid monohydrate 0.774 g Disodium hydrogen Orthophosphate anhydrous 1.793 g Distilled water to 100 ml.	6.08	6.00

A correct answer was taken to be one within 0.5 pH unit of the known pH of the solution. The number of correct answers given by the 20 anaesthetists when each paper was used to test each solution is shown in table III. The total number of correct answers for each paper is also expressed as a percentage of possible correct answers.

Paper 2 resulted in significantly fewer correct answers than the other papers ($P < 0.001$). Nine participants spontaneously remarked that it was most difficult to distinguish colour change in the pH range 3–6 with this paper.

Paper 5 gave significantly fewer correct answers than papers 1, 3 ($P < 0.001$) and 4 ($P < 0.01$). There was no significant difference in the number of correct answers given with papers 1, 3 and 4.

On questioning as to which paper was found easiest to read, 12 anaesthetists preferred paper 1, five paper 3 and two liked 1 and 3 equally. One found paper 5 easiest to read.

TABLE III. *The number of correct answers given when 20 anaesthetists read each pH paper for each solution*

	pH 2	pH 3	pH 4	pH 6	Total correct	% correct
Paper 1	16	15	20	20	71	88.75
Paper 2	0	14	0	2	16	20.0
Paper 3	17	19	19	19	74	92.5
Paper 4	13	17	19	17	66	82.5
Paper 5	20	12	14	3	49	61.25

DISCUSSION

Acid aspiration syndrome has been recognized as a cause of anaesthetic-associated mortality, and may occur without obvious regurgitation or vomiting in both general and obstetric practice (Mendelson, 1946; McCormick, 1966; Blitt et al., 1970; Harrison, 1978). It has been shown that the aspiration of fluid of pH less than 2.5 and of volume greater than 25 ml causes severe pulmonary damage (Mendelson, 1946; Teabeaut, 1952; Vandam, 1965), although a case of pulmonary damage occurring with an aspirate of pH 3.5 has been reported (Taylor, 1975). If regurgitation occurs, after intubation, the pH of the regurgitated fluid may be tested. If it is sufficiently low, treatment may be instituted which may prevent the onset of the acid aspiration syndrome or ameliorate its course.

pH can be very accurately measured using a pH electrode or complex indicator techniques based on the measurement of colour and utilizing absorptiometers and spectrophotometers. However, in the clinical situation, a rapid and simple method—which can be made available in the anaesthetic room—is more likely to be used and acted upon. Indicator paper, if accurate in this important range, would appear ideal.

This study has shown that the degree of accuracy obtained from five different papers varied widely, from a low of 20% to a maximum 92.5% correct answers. Two papers were shown to be accurate and were liked by those taking part in the study: the Camlab paper and the Merck (Acilit and Neutralit) strips. Both of those had a combination of three colour changes which were compared to obtain a result. Therefore, if one colour change was subtle, it was less important than with a single colour change paper. Of the single colour change papers, those giving a more definite colour change were easiest to read and gave more accurate values. The worst paper had only subtle shade changes in the test range, making it more difficult to distinguish differences in pH. This was remarked upon by almost half those participating in the testing (nine out of 20).

Both papers giving the best results were stored in plastic boxes—the Camlab paper as a reel, and the Merck papers as 100 strips per box, so both would be protected from damp and spillage on an anaesthetic machine. The use of a single test (Camlab) rather than a two-strip test (Merck) may be considered to be a marginal advantage.

In conclusion, if an indicator paper is to be kept in the anaesthetic room to test the pH of regurgitated fluid, it should be a paper known to give as high a degree of accuracy as possible when read by anaesthetists.

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ACUTE DILATATION OF THE STOMACH DURING GENERAL ANAESTHESIA

A Case Report

C. M. KUMAR AND P. G. P. LAWLER

SUMMARY

We describe a case of acute dilatation of the stomach which occurred during general anaesthesia for cataract extraction. This resulted in aspiration pneumonitis. We report the case because of its unexpected and sudden appearance. The presentation and management of this case is described, together with a review of the anaesthetic problems which may occur.

Although acute dilatation of the stomach was first described by Rokitansky in 1842 (Bockus, 1974), it receives only passing mention (if any) in standard textbooks of anaesthesia. However, since acute dilatation of the stomach may be complicated by hypovolaemic shock, electrolyte imbalance and aspiration pneumonia (Katz, Benumof and Kadis, 1981), it is of some importance to the practice of anaesthesia.

CASE REPORT

A 65-yr-old moderately obese (82-kg) man was scheduled for elective cataract operation under general anaesthesia. There was no history of systemic disease and he required no regular medication. His preoperative haemoglobin was 10.1 g dl^{-1}. His electrolyte concentrations were within normal limits.

One hour before operation, the patient was premedicated with papaveretum 15 mg, and atropine 0.6 mg, both i.m. He had been fasted since midnight and arrived in the anaesthetic room at 14.00 h. His immediate preoperative arterial pressure was 125/75 mm Hg and his heart rate was 75 beat min^{-1}. He was pre-oxygenated with 100% oxygen before the induction of anaesthesia (in the supine position) with thiopentone 275 mg. Intubation of the trachea was facilitated with suxamethonium 100 mg. During laryngoscopy, his pharynx was seen to be clear of secretions. His lungs were not ventilated manually at any time until intubation had been accomplished. Anaesthesia was maintained with oxygen, nitrous oxide and halothane and the patient breathed spontaneously via a Bain breathing system.

The ECG and arterial pressure were monitored throughout the procedure and remained stable. Towards the end of surgery, which lasted 25 min, a rattling noise was heard in the breathing system. This was thought to be caused most probably by sputum. However, tracheo–bronchial toilet disclosed a small quantity of dark coloured fluid in the suction catheter. Laryngoscopy revealed a large quantity of coffee ground fluid in the oropharynx. The mouth was cleared and a nasogastric tube passed. Approximately 750 ml of coffee ground material was aspirated. Auscultation of the chest revealed nothing untoward. The patient was allowed to recover consciousness in the left lateral position and the trachea was extubated once the patient was wide awake. Over the next 10 min, he became centrally cyanosed, and his conscious level deteriorated. Oxygen by face mask was continued. Auscultation of the chest revealed rhonchi and crepitations throughout both lung fields. While oxygen was continued, the patient received hydrocortisone 200 mg i.v. followed by aminophylline 250 mg over 5 min. His condition improved slowly.

He was transferred to the Intensive Therapy

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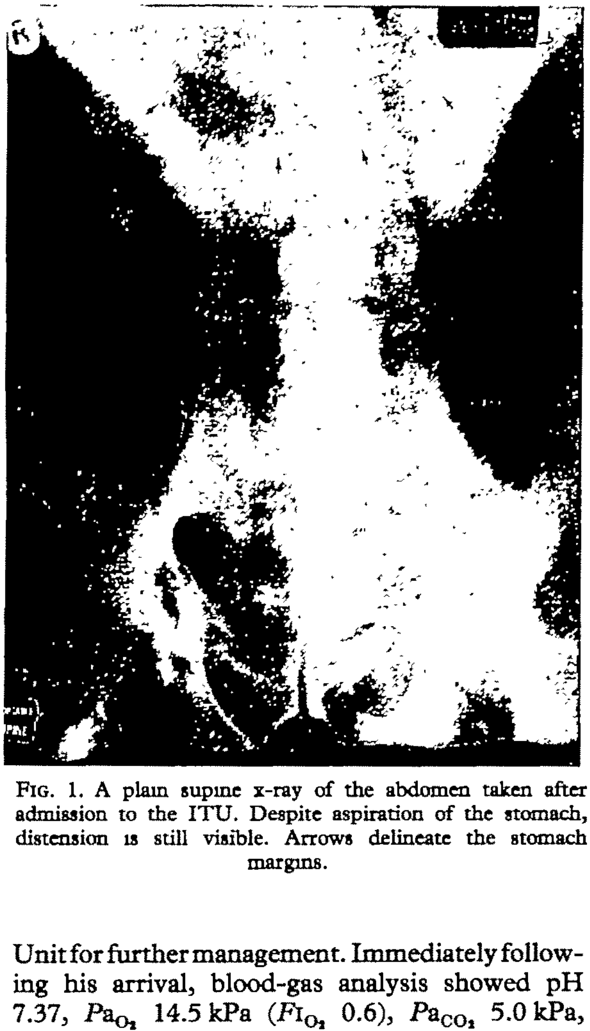

FIG. 1. A plain supine x-ray of the abdomen taken after admission to the ITU. Despite aspiration of the stomach, distension is still visible. Arrows delineate the stomach margins.

Unit for further management. Immediately following his arrival, blood-gas analysis showed pH 7.37, Pa_{O_2} 14.5 kPa (FI_{O_2} 0.6), Pa_{CO_2} 5.0 kPa, standard bicarbonate 26 mmol $litre^{-1}$ and base excess +2 mmol $litre^{-1}$. Electrolyte concentrations were within normal limits; albumin concentration was 35 g $litre^{-1}$. Haemoglobin concentration was 11.5 g dl^{-1}. A chest x-ray was clear. A plain x-ray of the abdomen, also taken soon after admission to the ITU, confirmed dilatation of the stomach (fig. 1). The pH of the gastric aspirate was 7.0. A further 1000 ml of gastric fluid was aspirated in the following 12 h.

The patient received prophylactic antibiotics, steroids, i.v. fluids and chest physiotherapy. A further chest x-ray, taken 12 h after admission to the ITU, showed bilateral widespread pulmonary infiltrates, compatible with aspiration. Nevertheless, the patient's general condition and blood-gas status improved. Twenty-four hours later his chest x-ray had completely cleared. The patient was transferred to the general ward on the same day and left the hospital well 5 days later.

DISCUSSION

The exact frequency of acute dilatation of the stomach is unknown (Scott, 1978). Nevertheless, it appears to have become less common since the widespread use of the nasogastric tube (Bockus, 1974). The majority of cases are reported to occur in the first few days following surgery (Scott, 1978), although it has been suggested that the condition may on occasions have been present for some time before its recognition (Bockus, 1974). While most patients appear to have developed the condition within hours of an operative procedure (Schwartz, 1964), it is not clear whether the dilatation has developed over minutes or hours (Morris, Ivy and Maddock, 1947).

Acute dilatation of the stomach may follow any operation (Rains and Ritchie, 1984). However, it is most commonly recognized following operation on the pelvic organs or the biliary tree (Scott, 1978). Other associated conditions include major trauma, stress, acute (severe) infections and diabetic ketoacidosis (Rains and Ritchie, 1984). Patients encased in an abdominal spica are also at risk (Rains and Ritchie, 1984). Distension of the stomach has been reported after ketamine anaesthesia (Tornos-Solano, 1971; Thompson, 1984). The excessive use of anticholinergic premedication has also been blamed (Wyngaarden and Smith, 1982). Nevertheless, on many occasions, there is no obvious cause (Castell and Jacoby, 1967; Chaun, 1969).

The mechanism of acute dilatation of the stomach is obscure (Scott, 1978). Aerophagia during anaesthesia might lead to the condition (Morris, Ivy and Maddock, 1947). Diffusion of nitrous oxide into the gastrointestinal tract (Foldes, Kepes and Ship, 1964) or postoperative oxygen therapy have also been blamed (Bockus, 1974). Manual ventilation of the lungs (with or without anaesthetic gases) could also lead to inflation of the stomach (Foldes, Kepes and Ship, 1965).

Whatever the cause, the stomach rapidly distends with both gas and mucoid secretions. The increase in intragastric pressure leads to mucosal congestion, which results in further secretion. Mucosal bleeding follows (Scott, 1978). Because of the development of a "third space", haemodynamic problems may occur (Isselbacher et al., 1980). However, these haemodynamic problems may also be the result of decreased venous return secondary to mechanical obstruction of the inferior vena cava, increases in portal venous pressure, presumably secondary to direct pressure on the portal vein, and possibly the result of post-sinusoidal obstruction resulting from high pressure in the vena cava (Berman et al., 1962; Mooney, Bryand and Griffen, 1969). A visceral–cardiac reflex has also been suggested as a cause of the haemodynamic disturbance (Williams, 1965).

The clinical presentation of acute dilatation of the stomach is variable (Schwartz, 1964; Bockus, 1974; Katz, Benumof and Kadis, 1981; Rains and Ritchie, 1984). The patient may complain of "muffled" hiccup, of epigastric fullness or of mild upper abdominal pain. He may suffer effortless vomiting of coffee-ground fluid. The physical signs include pallor, sweating, bradycardia or tachycardia and hypotension. Increasing epigastric distension, reduced bowel sounds, marked abdominal hyper-resonance, or a succussion splash may aid the diagnosis. A plain (erect) abdominal x-ray and aspiration of large quantities of gastric contents, perhaps coffee-ground, will confirm the diagnosis (Bockus, 1974).

Once the diagnosis has been made, nasogastric aspiration and restoration of fluid and electrolyte balance is required (Isselbacher et al., 1980). The stomach often requires a period of 1–2 days to regain normal activity, and during this period aspiration of the stomach should be continued (Castell and Jacoby, 1967).

The cause of the acute dilatation of the stomach in this patient is not clear. The patient gave no history of any systemic disease. He was not nervous. His premedication produced adequate (but not excessive) sedation. Atropine was used in low dose. In any event, atropine is widely prescribed, but acute dilatation of the stomach is rare. Manual ventilation of the lungs was not performed at any time before intubation so that inadvertent introduction of anaesthetic gases to the stomach (which might have initiated or produced the condition) did not occur. Aerophagia in the presence of the tracheal tube seemed unlikely but, because the face was covered by towels, it cannot be excluded. Foldes, Kepes and Ship (1965) described severe gastrointestinal distension occurring during nitrous oxide–oxygen anaesthesia. They considered nitrous oxide diffusion to be the causative factor. However, in their report, manual ventilation (with gases) had been used and they believed that this manoeuvre might have initiated the distension and that a vicious circle of nitrous oxide diffusion into the gut was then set up. There was a significant delay before distension occurred. In our patient, we believe that there had been insufficient time for diffusion of nitrous oxide to have taken place.

We cannot rule out the presence of acute dilatation of the stomach in the preoperative period and that this had remained unrecognized. This argument is supported by the absence of haemodynamic disturbance during anaesthesia. Suspicion was aroused only when rattling was heard in the breathing circuit. Tracheo–bronchial toilet revealed a small quantity of coloured fluid. Silent regurgitation and aspiration, despite the presence of a tracheal tube, was considered to have occurred (Blitt et al., 1970). Fortunately, at this stage in this operation, formal laryngoscopy could be performed, revealing a large quantity of gastric contents in the pharynx. Nasogastric aspiration, following passage of a nasogastric tube, suggested the diagnosis, and prevented massive soiling of the lungs.

We believe that the full blown haemodynamic picture did not develop because of the prompt recognition of the condition. We conclude that acute dilatation of the stomach may occur during any operation and may be of rapid onset although, in the patient reported, the distension may have been present before operation. There may be no obvious associated factor and the condition may go unrecognized. The chance of silent regurgitation (and possible aspiration) will be increased in the presence of acute dilatation of the stomach. The passage of a nasogastric tube whenever significant quantities of gastric secretions are found in the oropharynx during anaesthesia seems appropriate, both to exclude the diagnosis of acute dilatation of the stomach, and to reduce the likelihood of pulmonary aspiration.

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MALIGNANT HYPERPYREXIA AND ISOFLURANE

A Case Report

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SUMMARY

Malignant hyperpyrexia developed, and was successfully treated, in a 50-year old man undergoing pyelolithotomy. Early diagnosis with the assistance of end-tidal carbon dioxide monitoring facilitated prompt treatment with i.v. dantrolene. A positive muscle biopsy subsequently confirmed the diagnosis. The only likely triggering agent used was isoflurane.

Malignant hyperpyrexia is an inherited condition which may present during general anaesthesia as a progressive increase in body temperature associated with hypercapnia, metabolic acidosis and muscle rigidity. Halothane and suxamethonium are the most commonly suspected triggering agents.

CASE REPORT

A 50-yr-old man was admitted for pyelolithotomy. He was noted to be in good general health, although with a plethoric appearance, on the preoperative visit. His haemoglobin concentration was 17 g dl^{-1}; he was a smoker. He had received a dental anaesthetic in the 1950s. Temazepam 30 mg was prescribed as premedication.

Anaesthesia

Following the insertion of an appropriate cannula to a vein, anaesthesia was induced with sodium methohexitone 160 mg and maintained with nitrous oxide and isoflurane in oxygen. Tracheal intubation was facilitated with vecuronium 8 mg; muscle relaxation was adequate for this purpose. Fentanyl 100 µg was given at this stage and an extradural catheter inserted at T7. The patient was transferred to the operating table and positioned for surgery.

Monitoring consisted of an ECG, measurement of arterial pressure (Dinamap), end-tidal carbon dioxide concentration (Datex) and neuromuscular transmission. The patient's lungs were ventilated using a Manley ventilator, and the tidal volume monitored (Wright's respirometer).

Following the positioning of the patient, 10 ml of 0.5 % bupivacaine plain solution was injected to the extradural space. Figure 1 summarizes the subsequent course of the anaesthetic.

One hour following the induction of anaesthesia the patient was observed to be hypercapnic, the end-tidal carbon dioxide concentration having increased from its original value of 4.8 % to 6.0 %. It was thought at this stage to be a result of underventilation and, after extensive examination of the ventilator and the ventilator tubing, the minute volume was increased to 8 litre min^{-1} and, subsequently, to 12 litre min^{-1}. Calibration of the end-tidal carbon dioxide monitor was carried out and the carbon dioxide cylinder removed from the back of the anaesthetic machine to rule out inadvertent leakage into the fresh gas supply. The patient was noted to be sweating profusely and an axillary temperature was recorded as 37.5 °C. At the same time fentanyl 100 µg was given in case the sweating was caused by inadequate depth of anaesthesia. Additionally, vecuronium 2 mg was given. The end-tidal carbon dioxide concentration continued to increase; the temperature had now increased to 38 °C. A provisional diagnosis of malignant hyperpyrexia was made and the patient was given dantrolene 100 mg i.v. At the same time arterial blood-gas tensions and serum electrolyte concentrations were measured.

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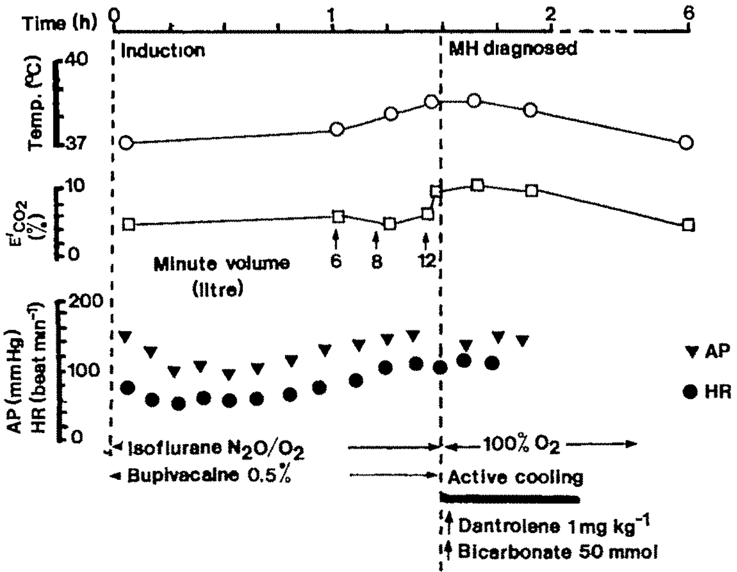

Arterial blood-gases

pH	7.23	7.31	7.36
Pa_{CO_2} (kPa)	8.6	6.2	5.7
Pa_{O_2} (kPa)	13.7	9.8	13.4
Bicarbonate	22	22	23
Base excess	-3	-3	-1

FIG. 1. Course of the anaesthetic.

Active cooling was undertaken with ice packs and the patient received sodium bicarbonate 50 mmol. Ventilation was continued with 100% oxygen and surgery was completed rapidly. The patient's temperature was now 38.5 °C and his end-tidal carbon dioxide concentration was over 10%. Initial blood-gas analysis showed a mild acidosis with a base deficit of −3 mmol litre^{-1} with a Pa_{CO_2} of 8.6 kPa. Repeat blood-gas analysis following the administration of bicarbonate and the dantrolene showed an improvement in arterial carbon dioxide concentration which had decreased to 6.2 kPa; the base deficit remained at −3 mmol litre^{-1}. By this time the patient was awake and, as he was distressed by the presence of the tracheal tube, the trachea was extubated and he breathed 40% oxygen via an anaesthetic face mask.

The patient was transferred to the Intensive Care Unit (ICU) for further management. His subsequent treatment involved ensuring a large volume urine output and careful monitoring of temperature. His serum creatinine phosphokinase (CPK) and urinary myoglobin concentrations were monitored for 3 days after operation (table I). The highest recorded CPK concentration was 1360 iu litre^{-1}; no myoglobin was detected in the urine.

He was discharged from the ICU on the 3rd day after operation, without any further hyperpyrexic episodes. The following day his temperature

TABLE I. *Concentrations of serum electrolytes, and myoglobin in the urine*

	Day of operation		Days after operation		
	Before op.	After op.	1	2	3
Serum potassium (mmol litre^{-1})	4.3	5.3	4.6	4.3	4.4
CPK (iu litre^{-1})	—	147	1360	554	367
Urinary myoglobin	—	nil	nil	nil	nil

began to increase once more. However, this was secondary to a wound infection. This infection resolved slowly; in other respects the patient made an uneventful recovery. Referral for follow-up muscle biopsy and related *in vitro* tests was made to the Malignant Hyperpyrexia Investigation Unit at St James's University Hospital, Leeds. These tests confirmed the patient's susceptibility to malignant hyperpyrexia. All investigations at this unit were carried out in accordance with the procedure accepted by the European Malignant Hyperpyrexia Group (Ellis et al., 1984).

DISCUSSION

The report describes the successful management of an episode of malignant hyperpyrexia. Several factors make it worth reporting.

The measurement of end tidal carbon dioxide concentration is a non-invasive method of detecting malignant hyperpyrexia in its early stages (Baudendistel et al., 1984). For some years capnographs have been available on every anaesthetic machine at this hospital. This case shows that in a hyperpyrexial episode it was a much more sensitive warning device than temperature.

The steady increase in end-tidal carbon dioxide concentration in the face of increasing minute volume was responsible for the prompt diagnosis and the treatment with dantrolene. As a result, the patient developed only a mild acidosis and a peak axillary temperature of 38.5 °C. Moreover, he exhibited only a minor increase in serum CPK concentration, and this may in part have been the result of prompt treatment.

Although the patient had received a previous dental anaesthetic, the details were unavailable. If malignant hyperpyrexia triggering agents were used at that time the duration of exposure may have been short and any mild metabolic disturbance could have passed undetected. Even in this case, if a capnograph had not been used, the diagnosis might have been delayed.

On this occasion isoflurane would appear to be the most likely trigger agent. Vecuronium was the only neuromuscular blocking drug used and there have been no reports of its implication as a triggering agent. Bupivacaine and nitrous oxide are probably safe to use, and are used in patients already known to be susceptible to malignant hyperpyrexia without complication. Although there have been two previous reports of malignant hyperpyrexia occurring in association with isoflurane, both patients had received suxamethonium and in neither patient was the diagnosis confirmed by muscle biopsy (Boheler et al., 1982; Joseph, Shah and Viljoen, 1982). In this case, the patient received a trigger-free anaesthetic, apart from the isoflurane. As the patient had a thoracic extradural catheter *in situ*, the inspired concentrations of isoflurane were low, perhaps explaining the slow development of the hyperpyrexia, and again illustrating the sensitivity of the monitoring of end-tidal carbon dioxide concentration in diagnosis.

Initial studies on isoflurane have shown that it can produce a three-fold increase in caffeine-induced contraction of the frog sartorius muscle at clinical concentrations (this compares with a four-fold increase for enflurane and an 11-fold increase with halothane (Wade and Wendell, 1981)). It is, therefore, not surprising that it can cause malignant hyperpyrexia in man.

This would appear to be the most convincing report of isoflurane-induced malignant hyperpyrexia. The fortuitous use of a technique in which isoflurane was the only likely triggering agent enables this conclusion to be reached.

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BOOK REVIEW

A Colour Atlas of Cardiopulmonary Resuscitation Techniques, 1st Edn. By G. Page, K. Mills and R. Morton. Published by Wolfe Medical Publications Ltd. Pp. 96; indexed; illustrated. Price £9.95.

As the title implies, this book is indeed an atlas. It has 96 glossy pages containing no less than 200 high quality coloured photographs of procedures and equipment, each accompanied by some explanatory text. The authors are a Consultant in Accident and Emergency Care and a Consultant Orthopaedic Surgeon both from Aberdeen, and a Professional Photographer. The book measures 26 cm × 19 cm × 0.75 cm, is presented with soft covers, and costs £9.95.

There are five sections: two short ones dealing with the aetiology and diagnosis of cardiorespiratory arrest, followed by 50 pages on basic life support, 16 pages on advanced life support, and five pages on extrication. The index covers three pages.

The book proceeds alphabetically through the A, B, C and D, E, F of cardiopulmonary resuscitation. Basic life support includes A for airway control, B for breathing support and C for circulation support, while advanced life support includes D for drip and drug administration, E for electrocardiographic diagnosis and F for fibrillation treatment.

The authors state in their preface that this atlas is intended to help medical practitioners, nurses, off-shore medics, ambulance personnel, police, firemen and first aiders, to manage cardiopulmonary resuscitation. They have tried to illustrate "a wide variety of different methods" in the various sections of the book, and they realize that not all of them will find favour in different centres.

In Basic Life Support the first section, on airway control, comprehensively covers the clearance and maintenance of the airway in unconscious patients without the use of any equipment. This is followed by advice on the oro-pharyngeal airway and the oesophageal obturator airway. The latter will be unfamiliar to many people in this country, and I would question its inclusion in a book of this type. Endotracheal intubation is described in some detail and cricothyrotomy is demonstrated using a 12-gauge cannula. Regrettably, no mention is made of the the mini-tracheostomy sets which are currently available. This section concludes with photographs of a formal surgical tracheostomy and the longer term care of patients with indwelling tracheal tubes, both of which could have been excluded.

The second section, on breathing support, begins with oxygen therapy which, surprisingly, comes before the maintenance of ventilation by expired air techniques. Undue emphasis is placed on the risks of high inspired oxygen percentages in the emergency resuscitation situation, while no indication is given of the minimum safe flow rates for the M.C. mask which is shown in the photograph—a mask which is currently being superseded in many emergency services by more comfortable and robust types.

The insertion of a chest drain is shown stage-by-stage using a trocar and cannula and a Malecot catheter. No reference is made to clear plastic drains, with their own introducer, which are commonly used in the emergency situation. It came as a surprise to see the familiar plastic receptacle of a standard theatre suction unit recommended for use as an underwater seal bottle. Equally surprising was the use of pressure tubing to connect it to the chest drain, and although a warning is given against the use of excessive suction, there is no indication of the use of any safety device to limit this.

The third section, on circulatory support, includes a particularly clear photograph showing the landmarks for pericardial paracentesis. This precedes some photographs of the first aid control of external haemorrhage and a brief mention of the military anti-shock suit. The section concludes with an attempt to cover shock in four pages of text.

Advanced life support begins with how to establish a peripheral i.v. infusion both percutaneously and by cut-down, and also how to insert a central line using the infra-clavicular approach to the subclavian vein. Radial artery puncture is shown, but the use of a 21-gauge needle attached to a 10-ml glass syringe will raise a few eyebrows, if not haematomata—at least among anaesthetists.

Finally, there are displays of ECG patterns in cardiac arrest, followed by details of defibrillation.

This book is a curious mixture, attempting as it does to cover all aspects of cardiopulmonary resuscitation from how to stop a bleeding forehead wound by pressing on it with a swab to internal—yes, internal!—cardiac massage and external defibrillation. In general, the more basic the technique the better it is described, and there are many points of detail in the more complex procedures which may not find favour in anaesthetic circles. Indeed, it has to be said that the book is unlikely to be purchased by trainee anaesthetists or to find a place on the intensive care unit bookshelf. It should, however, prove to be a useful adjunct to formal teaching for ambulancemen and off-shore medics, especially with the increasing interest in the extended role of the ambulanceman at the present time.

A. B. M. Telfer

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